Clinical Practice Guideline on Acute Bronchiolitis

CLINICAL PRACTICE GUIDELINES IN THE SPANISH NATIONAL HEALTHCARE SYSTEM

MINISTRY FOR HEALTH AND SOCIAL POLICY

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This CPG is an aid for healthcare decisions. It is not binding, and does not replace the clinical judgement of healthcare staff.

Published: 2010
Published by: Ministry for Science and Innovation
NIPO (Official Publication Identification No.): 477-09-055-4
ISBN: pending
Legal depository: B-10297-2010
Printed by: Migraf Digital

This CPG has been funded via an agreement entered into by the Carlos III Health Institute, an autonomous body within the Spanish Ministry for Science and Innovation, and the Catalan Agency for Health Technology Assessment, within the framework for cooperation established in the Quality Plan for the Spanish National Healthcare System of the Spanish Ministry for Health and Social Policy.

This guideline must be cited:
Working Group of the Clinical Practice Guideline on Acute Bronchiolitis; Sant Joan de Déu Foundation Fundació Sant Joan de Déu, coordinator; Clinical Practice Guideline on Acute Bronchiolitis; Quality Plan for the Spanish National Healthcare System of the Spanish Ministry for Health and Social Policy; Catalan Agency for Health Technology Assessment, 2010; Clinical Practice Guidelines in the Spanish National Healthcare System: CAHTA no. 2007/05.

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Presentation

Medical practice is becoming more and more complex for several reasons. One of the main reasons is the exponential increase in scientific information. In order for clinical decisions to be appropriate, efficient and safe, professionals need to update their knowledge continually. Major efforts are made to achieve this.

In 2003, the Inter-Regional Council of the Spanish National Healthcare System created a project known as GuíaSalud. This aims to improve clinical decisions based on scientific evidence via training activities and by establishing a register of Clinical Practice Guidelines (CPGs) within the Spanish National Healthcare System. Since then, the GuíaSalud project has evaluated dozens of CPGs according to explicit criteria established by its scientific committee, and it has registered them and disseminated them via the Internet. In early 2006, the Management Body of the Quality Agency of the Spanish National Healthcare System developed a Quality Plan for the Spanish National Healthcare System, based on twelve strategies. The Quality Plan aims to increase cohesion within the Spanish National Healthcare System, and to help ensure that the healthcare received by all members of the public is of the utmost quality, regardless of where they live. As part of the Plan, compilation of eight CPGs was assigned to various agencies and groups of experts in common disorders related to health strategies. This guideline on acute bronchiolitis is one of the CPGs assigned.

The task of establishing a common methodology for compiling CPGs for the Spanish National Healthcare System was also assigned. This methodology was developed by joint consensus and coordination between groups of CPG experts in Spain.

The GuíaSalud project was renewed in 2007 with the creation of the Library of Clinical Practice Guidelines. This project examines the development of CPGs in more detail and includes other services and products of evidence-based medicine. It also aims to encourage implementation and evaluation of the use of CPGs in the Spanish National Healthcare System.

Acute bronchiolitis is the most common infection of the lower respiratory tract in infants, and its incidence has increased in recent years. It generates substantial demand for healthcare. There is also scientific disagreement as to how bronchiolitis should be handled, leading to major variation in how it is treated. This is why bronchiolitis has been selected as the subject of a CPG.

The aim of this CPG is to provide the public and healthcare professionals with a useful tool that provides answers to the questions raised by this illness, particularly regarding prevention, diagnosis and treatment. It also aims to provide carers with information that enables them to understand the illness affecting their child better, and to deal with it with greater peace of mind.

This CPG was developed by a group of Spanish experts in childhood respiratory disorders and evidence-based medicine. It has been endorsed by patients' parents and Spanish scientific societies which are involved in the care of these patients.

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Director of the Quality Agency
of the Spanish National Healthcare SystemAuthorship and Collaboration

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This CPG is endorsed by the following bodies:

Spanish Paediatrics Association (AEP)

Spanish Society for Paediatric Respiratory Medicine (SENP)

Spanish Society for Neonatology (SEN)

Spanish Association for Paediatric Primary Care (AEPap)

Spanish Society for Outpatient Paediatrics and Primary Care (SEPEAP)

Spanish Society for Paediatric Intensive Care (SECIP)

Spanish Society for Paediatric Emergency Care (SEUP)

Disclosure of interests: The disclosures of interests attached as **Appendix 5** have been provided by all members of the Working Group and those who took part in expert collaboration, development of materials for patients and external review.

The development of this document was not affected by the points of view or interests of those who provided funding.

Questions to Answer

DIAGNOSIS

1. In patients with acute bronchiolitis, what clinical severity criteria can be considered for the progression of bronchiolitis?
2. In patients with acute bronchiolitis, are assessment scales useful in taking decisions? What scales should be used?
3. In patients with acute bronchiolitis, what criteria may be useful in deciding whether to refer patients from primary and outpatient care to hospitals?
4. In patients with acute bronchiolitis, what criteria may be useful in deciding whether patients need to be admitted to hospital?
5. In patients with acute bronchiolitis who need to be admitted to hospital, what criteria may be useful in deciding whether they need to be admitted to Paediatric Intensive Care Units (PICUs)?
6. In patients with acute bronchiolitis, what criteria may be useful in deciding when to discharge patients from hospital?
7. In patients with acute bronchiolitis, what are the associated microorganisms?

ADDITIONAL EXAMINATIONS

8. In patients with acute bronchiolitis, when are blood counts, C-reactive protein (CRP) assays, procalcitonin (PCT) assays and/or blood cultures needed?
9. In patients with acute bronchiolitis, when are urine tests and/or urine cultures needed?
10. In patients with acute bronchiolitis, when are blood gas tests needed and what type is required?
11. In patients with acute bronchiolitis, when are chest X-rays needed?
12. In patients with acute bronchiolitis, when do associated viruses need to be investigated?
13. In patients with acute bronchiolitis in whom RSV infection is investigated, what laboratory technique should be used?

TREATMENT

14. In patients with acute bronchiolitis, what is the arterial oxygen saturation threshold, measured via pulse oximetry, for administering oxygen?
15. In patients with acute bronchiolitis, are nebulised bronchodilators (salbuta-mol, terbutaline, adrenaline, ipratropium bromide, xanthines) beneficial?
16. In patients with acute bronchiolitis, is there another useful route of administration for any bronchodilator?
17. In patients with acute bronchiolitis, is nebulised rhDNase, saline solution or hypertonic solution useful?
18. In patients with acute bronchiolitis, are mucolytics, antitussives and nasal decongestants useful in improving clinical presentation and progression?
19. In patients with acute bronchiolitis, are antibiotics useful in improving clinical presentation or progression?
20. In patients with acute bronchiolitis with atelectasis and/or images of alveolar involvement, are antibiotics useful?
21. In patients with acute bronchiolitis, is a helium/oxygen gas mixture useful in improving clinical presentation or progression?
22. In patients with acute bronchiolitis, is a mixture of helium and oxygen, rather than air and oxygen, pure air or pure oxygen, useful as a drug nebulisation medium to improve distal drug availability or response to the drug?
23. In patients with acute bronchiolitis, is glucocorticoid treatment safe and effective in improving clinical presentation and progression?
24. In patients with acute bronchiolitis who have required tracheal intubation, are glucocorticoids useful in reducing intubation time?
25. In patients with acute bronchiolitis, are antivirals useful in preventing contagion or improving clinical presentation or progression?
26. In patients with acute bronchiolitis, does montelukast improve clinical presentation or progression?
27. In patients with acute bronchiolitis, are aspiration of secretions, humidification and positional measures useful in improving clinical presentation or progression?
28. In patients with acute bronchiolitis, does breaking up feeds, thickening feeds, tube feeding or giving nil by mouth and hydrating intravenously improve clinical presentation or progression?
29. In patients with acute bronchiolitis, is respiratory physiotherapy useful in improving clinical presentation or progression?
30. In patients with acute bronchitis who require hospitalisation, are non-invasive ventilation in the form of CPAP (continuous positive airway pressure) or other methods useful in improving clinical presentation and progression?

31. In patients with acute bronchiolitis, when is conventional mechanical ventilation indicated?
32. What other treatments have been tried in patients with acute bronchiolitis, and what have been the results?

MONITORING

33. In patients with acute bronchiolitis, when is continuous or occasional oxygen saturation monitoring via pulse oximetry indicated?
34. In patients with acute bronchiolitis, when is continuous or occasional CO_2 monitoring (transcutaneous or exhaled) indicated?
35. In patients with acute bronchiolitis, when is monitoring of BR, HR and a clinical severity scale indicated?
36. In patients with acute bronchiolitis, when is apnoea monitoring indicated?

PREVENTION

37. In children aged under 24 months, are anti-RSV monoclonal antibodies useful in preventing the onset of bronchiolitis or in reducing clinical severity if it develops? Are they particularly indicated for a specific population or a high-risk population?
38. In what patients is it viable, in terms of cost/benefit, to administer anti-RSV monoclonal antibodies in order to prevent acute bronchitis? Is it viable to administer them as treatment during the acute phase?
39. What measures are useful in preventing community transmission of RSV and other respiratory viruses?
40. What measures are useful in preventing hospital transmission of RSV and other respiratory viruses?
41. In patients with acute bronchiolitis, what is the relationship between maternal smoking during pregnancy and passive exposure of children to tobacco smoke and the incidence and severity of the illness?
42. In patients with acute bronchiolitis, what is the relationship between breastfeeding and the incidence and severity of the illness?
43. In patients with acute bronchiolitis, what is the relationship between prematurity, birthweight, mother's age, number of siblings, time of year, patient's chronological age at the beginning of the respiratory virus season, nursery school attendance and comorbidities with the incidence and severity of the illness?

PROGRESSION

44. What is the usual duration of signs and symptoms in patients with acute bronchiolitis? What percentage of patients with acute bronchiolitis are admitted to hospital? Of these, how many are admitted to PICUs?
45. Do patients with acute bronchiolitis have a higher risk of developing recurrent wheezing/asthma?
46. In patients with acute bronchiolitis, do anti-RSV monoclonal antibodies reduce the risk of developing recurrent wheezing/asthma?

Summary of Recommendations

Grade of recommendation: A, B, C or D, depending on whether the quality of the evidence is very good, good, average or poor (**Appendix 1**).

• Good clinical practice: recommendation based on consensus of the working group.

Diagnosis

Clinical severity criteria and risk factors	
A	The following are considered to be clinical severity criteria for the progression of bronchiolitis: • Refusal to feed or digestive intolerance, • Lethargy, • History of apnoea, • Tachypnoea for the patient's age, • Nasal flaring, severe retractions, grunting, cyanosis.
B	The following are considered to be risk factors for severe bronchiolitis: • Age under 12 weeks, • The following comorbidities: haemodynamically significant congenital heart disease, immunodeficiency, chronic lung disease, prematurity;
C	• Rapid onset (< 72 hrs), • Smoking around the child, • Higher number of siblings and nursery attendance, • Overcrowding and poverty, • No breastfeeding, • Down's syndrome, • Neuromuscular disease;
D	• Low birth weight (< 2,500 g [5.5 lb]), • Young mother, • Younger age at the beginning of the RSV season.
D	There is insufficient evidence to conclude whether or not the following are risk factors for severity: • A specific aetiology, • A specific type of RSV (A or B), • High RSV viral load in the nasopharynx, • Some genetic polymorphisms.

C	Atopy has not been shown to be a risk factor for severity.
√	The airways should be unblocked before the severity of a patient's condition is assessed.
Severity scales	
√	Although there are as yet no validated scales for the purpose, ideally the severity of patients with acute bronchiolitis should be assessed uniformly, using a scale.
√	The airways should be unblocked before the severity of a patient's condition is assessed.
Criteria for referral from primary and outpatient care to hospitals	
√	Patients with the following symptoms should be referred to hospital: • Refusal to feed or digestive intolerance (approximate intake less than 50% of usual intake), • Dehydration, • Lethargy, • History of apnoea, • Tachypnoea for the patient's age, • Moderate or severe respiratory difficulty (grunting, nasal flaring, retractions or cyanosis), • Oxygen saturation < 92-94% when breathing ambient air, • Severe illness according to the scale used, • Uncertain diagnosis.
√	The following factors should be taken into account when referring a patient to hospital: • Age (< 2-3 months), • Comorbidities, • Symptom onset < 72 hrs, due to risk of deterioration, • Socioeconomic status of the patient's environment, geographical factors, transport difficulties, • Parents' or carers' ability to assess the severity of the child's condition.
√	Parents should be provided with information on how to handle acute bronchiolitis and grounds for repeat consultation.

Criteria for hospital admission	
√	Patients with the following symptoms should be admitted to hospital: • Age under 4-6 weeks, • Refusal to feed or digestive intolerance (approximate intake less than 50% of usual intake), • Dehydration, • Lethargy, • History of apnoea, • Tachypnoea for the patient's age, • Moderate or severe respiratory difficulty (grunting, nasal flaring, retractions or cyanosis), • Oxygen saturation < 92% when breathing ambient air, • Comorbidities: clinically significant heart disease, pulmonary hypertension, neuromuscular disease, oxygen-dependent lung disease, immunodeficiency, • Uncertain diagnosis.
√	The following factors should be taken into account when deciding whether to admit a patient to hospital: • Other comorbidities: heart disease, chronic lung disease, history of prematurity, Down's syndrome, • Symptom onset < 24-48 hrs with rapid symptom progression, • Socioeconomic status of the patient's environment, geographical factors, transport difficulties, • Parents' or carers' ability to assess the severity of the child's condition.
Criteria for PICU admission	
√	PICU admission is indicated if oxygen saturation cannot be maintained despite increased oxygen therapy, if respiratory status deteriorates with signs of increasing respiratory distress or signs of exhaustion, or if the patient presents recurrent apnoea.
Discharge criteria	
√	Monitoring must be continued for approximately 8-12 hrs after oxygen is withdrawn, including during a period of sleep.
√	Discharge should be planned from admission onwards (agree discharge criteria with parents on admission).

√	A patient can be discharged when: • BR is appropriate for the patient's age, with no clinical evidence of increasing respiratory distress, • SpO_2 is 94% when breathing ambient air, • Food intake is adequate, • Carers are able to clear the airways, • Resources in the environment are appropriate (parents/carers provided with accurate information on progression and grounds for repeat consultation, parents/carers consent to the discharge, suitable follow-up possible).
Aetiological agents	
B	Acute bronchiolitis is associated with viral respiratory infections.
C	To date it has been described in association with the following: RSV (main cause), rhinovirus, enterovirus, adenovirus, metapneumovirus, influenzas, parainfluenza, bocavirus. Concurrent viral infections have been described. An association with Mycoplasma pneumoniae has also been described.
D	Progression and severity may depend on the virus associated with bronchiolitis, but to date there is insufficient evidence of this.
D	Healthcare professionals must bear in mind the time of year when making diagnoses. In Spain, bronchiolitis has a seasonal peak (autumn and winter).

Additional Examinations

Blood counts, C-reactive protein (CRP) assays, procalcitonin (PCT) assays and/or blood cultures	
D	Routine blood counts, CRP assays and/or PCT assays are not recommended in patients with typical acute bronchiolitis.
D	Determining CRP and/or PCT levels may be useful in patients with acute bronchiolitis and fever in whom a potentially serious bacterial infection is suspected.
C	Routine blood bacteria tests are not indicated in children with typical acute bronchiolitis and no fever. Their use in patients with fever must be assessed on a case-by-case basis.
Sediment and/or urine culture	
C	Routine urine bacteria tests are not indicated in children with typical acute bronchiolitis and no fever.
√	The possibility of a urinary infection must be considered in patients aged under 3 months with acute bronchiolitis and fever.
Blood gas tests	
√	Routine blood gas tests (capillary or arterial) are not recommended for patients with acute bronchiolitis.
√	Blood gas tests (capillary or arterial) may have a role to play in the assessment of patients with severe respiratory difficulties who may be entering respiratory failure.
√	Determining transcutaneous SpO_2 and CO_2 pressure may be useful in establishing the blood gas status of patients with acute bronchiolitis non-invasively.
Chest X-rays	
A	Routine chest X-rays are not recommended for patients with typical acute bronchiolitis.
B	Chest X-rays should be reserved for patients whose diagnoses are uncertain and those with atypical clinical presentation, severe processes or unfavourable progression.
C	Chest X-rays are not useful in distinguishing between bacterial and viral infections.
A	Chest X-rays increase the unnecessary use of antibiotics.

Virus tests	
B	Routine virus tests are not recommended in the assessment of patients with acute bronchiolitis, as they do not affect their treatment.
A	RSV tests may be useful in establishing hospital cohorts when patients cannot be isolated.
√	Identifying respiratory viruses in patients with acute bronchiolitis may be of epidemiological interest.
D	To date, identifying other respiratory viruses does not appear to be useful in handling patients with acute bronchiolitis.
√	Ideally, all patients with acute bronchiolitis should be isolated. If this is not possible, cohorts should be established for all the viruses that can be identified.
D	If RSV identification is considered necessary to establish hospital cohorts and this occurs during an epidemic, rapid diagnostic tests may be used.
√	Molecular techniques may be useful for research studies or cases in which a patient's diagnosis is uncertain.

Treatment

Oxygen	
√	A decision to administer oxygen must be based on assessment of both signs of respiratory difficulty and oxygen saturation measured by pulse oximetry.
√	Children with severe respiratory difficulty and/or cyanosis and/or $SpO_2 < 92\%$ must be given additional oxygen.
√	Consider withdrawing additional oxygen when SpO_2 remains steady at > 94% when breathing ambient air.
√	Oxygen should be prepared appropriately (warmed and humidified).
Bronchodilators	
A	Routine $ß_2$-adrenergic agonist bronchodilating treatment is not recommended for acute bronchiolitis.
C	Nebulised ipratropium bromide is not recommended for the treatment of acute bronchiolitis.
A	Nebulised adrenaline is not recommended as routine treatment for acute bronchiolitis in children.

B	If a bronchodilator is considered necessary, therapeutic testing is recommended. Treatment should only be continued if there is a clinical response.
√	Xanthines, oral terbutaline, subcutaneous adrenaline, oral salbutamol and intravenous salbutamol are not recommended for patients with acute bronchiolitis.
D	Xanthines may be useful in treating apnoea associated with acute bronchiolitis in ex-premature infants.
Nebulised hypertonic solution and rhDNase	
A	3% nebulised saline solution in patients admitted to hospital with acute bronchiolitis, nebulised either alone or with bronchodilators and in repeated doses, is a useful treatment in reducing the length of hospitalisation. It is therefore recommended.
A	rhDNase is not recommended for patients with acute bronchiolitis.
Mucolytics, antitussives and nasal decongestants, alternative therapies and other treatments that have been tested in acute bronchiolitis	
B	Mucolytics, antitussives and nasal decongestants are not recommended for the treatment of acute bronchiolitis.
D	Antihistamines, oral decongestants, nasal vasoconstrictors, steam and alternative therapies such as homoeopathy are not recommended for patients with acute bronchiolitis.
C	Nebulised furosemide is not recommended for patients with acute bronchiolitis.
A	There is insufficient evidence to recommend the use of surfactants.
Antibiotics	
A	Antibiotics should not be used as routine treatment for acute bronchiolitis.
B	There is insufficient evidence on the value of macrolides in acute bronchiolitis. Their use is not recommended.
B	When there is a bacterial infection (e.g. a urinary infection or acute otitis media), this must be treated as it would be if the patient did not have bronchiolitis.
D	In patients with severe acute bronchiolitis requiring mechanical ventilation, a significant percentage have a concurrent bacterial lung infection. The use of antibiotics in these patients should be considered.
B	Antibiotics should not be used as routine treatment for bronchiolitis patients with atelectasis or alveolar involvement.
√	Antibiotics should be considered for patients with acute bronchiolitis who present clinical signs of severity and/or blood count, CRP and/or PCT alterations.

Heliox	
D	Heliox may be useful in patients with moderate to severe bronchiolitis, but more studies confirming this are needed.
√	Heliox as a drug nebulisation medium may improve the quantity of the drug that penetrates distally and drug distribution, but there are no specific studies involving patients with acute bronchiolitis.
Glucocorticoids	
A	Glucocorticoids are not recommended for the treatment of acute bronchiolitis, in any dosage form.
B	Routine use of glucocorticoids is not recommended for patients with acute bronchiolitis who are being mechanically ventilated.
Antivirals	
B	Ribavirin is not recommended for patients with acute bronchiolitis.
√	Ribavirin may have a role to play in severely immunocompromised patients with RSV infection.
Montelukast	
B	Montelukast treatment is not recommended for patients with acute bronchiolitis.
Supportive treatment, hydration and nutrition	
√	Respiratory secretions should be aspirated before feeds, before each inhaled treatment and when signs of obstruction of the upper airways are detected (audible evidence of secretions, increased distress).
√	Saline solution drops may be used before secretions are aspirated.
√	Respiratory secretions should be aspirated before the severity of a patient's condition is assessed.
√	Humidification has not been shown to be useful in patients with acute bronchiolitis. It is therefore not recommended.
√	Positional measures (lifting the head of the cot) are recommended for patients with acute bronchiolitis.
D	The hydration and ability to take liquids of patients with acute bronchiolitis must be assessed.
D	Feeds should be broken up and/or thickened if feeding difficulties are detected.
D	Feeding via nasogastric tube may be an option for children at risk of dehydration or with progressive respiratory difficulties.
√	In children whose condition is most severe, particularly those whose illness progression may require endotracheal intubation, intravenous hydration is recommended.

B	Patients with acute bronchiolitis may present the syndrome of inappropriate anti-diuretic hormone secretion.
Respiratory physiotherapy	
A	Respiratory physiotherapy is not recommended for patients with acute bronchiolitis.
Non-invasive ventilation and conventional ventilation	
B	CPAP non-invasive ventilation is effective in patients with acute bronchiolitis who present severe respiratory difficulties, hypercapnia or recurrent apnoea.
B	CPAP non-invasive ventilation has few side effects and is well tolerated.
√	Non-invasive ventilation must be considered for acute bronchiolitis patients with respiratory insufficiency despite medical treatment.
√	Mechanical ventilation must be considered for acute bronchiolitis patients with respiratory insufficiency, those with apnoea, those in whom other measures, such as non-invasive ventilation (NIV), have failed and those with signs of imminent arrest.
√	High-frequency oscillatory ventilation (HFOV) appears to be useful in patients with hypercapnic respiratory insufficiency despite conventional mechanical ventilation.

Monitoring

Pulse oximetry	
C	Oxygen saturation should be determined via pulse oximetry (SpO_2) during initial examination of patients with acute bronchiolitis.
D	When a child's clinical presentation improves, it is no longer necessary to monitor SpO_2 continuously.
B	Children with high-risk comorbidities (haemodynamically significant congenital heart disease, pulmonary hypertension, neuromuscular disease, oxygen-dependent lung disease and immunodeficiency) require more monitoring when their oxygen is being withdrawn.
CO_2 monitoring	
√	It may be useful to determine the CO_2 levels of patients with moderate or severe acute bronchiolitis non-invasively, particularly in patients receiving ventilatory support.

Heart rate (HR), breathing rate (BR), severity scale	
B	HR and BR should be monitored, particularly during the acute phase of the illness.
√	Using a severity scale may be useful in monitoring clinical progression and response to treatment in patients with acute bronchiolitis.
Monitoring apnoea	
D	Apnoea should be monitored in bronchiolitis patients aged under 1 month, those with a history of prematurity and those in whom a previous episode of apnoea is reported.

Prevention

Palivizumab	
A	Palivizumab reduces the number of hospital admissions due to RSV in high-risk patients. It has not been shown to reduce the incidence of the illness; the duration of hospitalisation, oxygen therapy or mechanical ventilation; or mortality.
A	Palivizumab prophylaxis is considered advisable for the prevention of severe lower respiratory tract diseases that require hospitalization, caused by RSV during the periods when there is an expected risk of infection due to RSV, in: • Children under 2 years who have required treatment for bronchopulmonary dysplasia in the last 6 months. • Children under 2 years with haemodynamically significant congenital heart disease. • Infants born at 35 weeks' gestation or less, who are 6 months old at the start of the RSV season or who are discharged from hospital during the RSV season.

C	In cases for which palivizumab prophylaxis is indicated, it should be administered from October to March as a monthly intramuscular dose of 15 mg/kg.
D	In patients for whom it is indicated, home administration of palivizumab may improve compliance and reduce the number of hospital admissions due to RSV.
A	Palivizumab has not been shown to be effective in treating established RSV infections.
√	Palivizumab reduces the rate of hospital admission due to RSV but does not prevent infection in all cases. It does not prevent other viral infections related to acute bronchiolitis. Hygiene measures must therefore be emphasised.
Measures to prevent community transmission	
D	Carers should be informed of the benefits of washing their hands in order to prevent transmission of respiratory viruses. They should be advised to wash their hands frequently.
D	Numbers of visits should be limited, particularly visits to very small and premature infants.
D	Contact with people with symptoms of respiratory infections and environments with a high risk of contagion should be avoided.
D	Tobacco exposure should be avoided. Carers should be informed that tobacco particles that cling to clothing may harm children even if no one smokes around the child.
√	Parents must be informed of these preventive measures before children are discharged from hospital, at birth and at follow-up visits up to the age of 1 year.
D	Carers should be educated on the signs and symptoms of acute bronchiolitis.
Measures to prevent hospital transmission	
D	RSV is highly contagious and penetrates the body through the mucous membranes of the eyes, nose or mouth. It is transmitted in secretions on the hands or on fomites, where it can survive for 6-12 hours. Droplets of secretions may be scattered up to 2 metres. RSV is destroyed by soap and water or alcohol gel.
D	Medical staff and those accompanying patients must be informed of the routes of transmission and control measures.
B	Hand-washing is the most important measure in preventing hospital transmission of RSV. Hands must be decontaminated before and after direct contact with patients, after contact with inanimate objects from the patient's surroundings and after removing gloves. Alcohol gels are recommended to disinfect the hands.
D	Contact measures (particularly doctor's coats and disposable gloves) are recommended.
D	Surfaces that come into contact with patients with acute bronchiolitis and medical materials from their surroundings should be disinfected.

D	Patients with acute bronchiolitis should be isolated. If this is not possible, hospital cohorts should be established by aetiology.
D	Visits by people with symptoms of respiratory infections should be restricted.
D	Compliance with control measures must be monitored.
D	Hand disinfection and isolation of contact, closure of units (closure to new admissions and restrictions to entry), establishing cohorts and palivizumab appear to be useful in controlling outbreaks of RSV infection in Neonatal Intensive Care Units.
Smoking	
C	Maternal smoking during pregnancy seems to increase the risk of acute bronchiolitis. Smoking should be avoided during pregnancy.
A	Exposure to tobacco smoke increases the rate of hospital admission due to lower respiratory tract infections, including bronchiolitis.
D	Exposure to tobacco smoke exacerbates symptoms and worsens the prognosis of patients with acute bronchiolitis.
Breastfeeding	
A	Breastfeeding protects infants against lower respiratory tract infections, including bronchiolitis.
A	Breastfeeding for more than 4 months offers greater protection against lower respiratory tract infections.
D	Breastfed infants seem to be at less risk of acute bronchiolitis and less risk of severity if it does develop.

Progression

Duration of clinical presentation, hospital admission rate	
B	Up to 70% of all children contract an RSV infection before the age of 1 year. 22% develop symptoms.
C	Approximately 13% of children develop acute bronchiolitis before the age of 1 year.
C	2-5% of infants require hospitalisation for acute bronchiolitis before the age of 1 year.
C	3% of children seen in Accident & Emergency wards and up to 20% of inpatients may be admitted to PICUs.
B	The usual duration of symptoms is 12 days (although 9% may still present symptoms at 28 days), but only 6-7 days of respiratory difficulty and feeding difficulties.
B	It should be explained to parents/carers that acute bronchiolitis may take several weeks to resolve.
D	Among those admitted to hospital, the average duration of hospitalisation is given as approximately 3 days, with an average of 56 hours' oxygen therapy.
D	Up to 20% of viral tests have been found positive 3 weeks after symptom onset.
Recurrent wheezing	
A	Patients with acute bronchiolitis may present recurrent wheezing.
A	Recurrent wheezing is more common up to the age of 5 years. Incidence falls as patients' age increases.
D	It is not known whether recurrent wheezing is secondary to damage done by the infection that causes acute bronchiolitis or if there is a prior genetic or environmental predisposition.
D	Palivizumab prophylaxis in premature infants may reduce the incidence of recurrent wheezing, but more studies demonstrating this are required.

1. Introduction

Acute bronchiolitis is the most common lower respiratory tract infection in infants[1,2]. Its annual incidence in infants is 10%[3], with a hospital admission rate of between 2% and 5%[3]. This has increased significantly in recent years[3,4].

In 1993, McConnochie established clinical criteria to define bronchiolitis[5]: first acute episode of wheezing in a child aged under 24 months, expiratory dyspnoea and prodromal cold[5]. However, the criteria used by different hospitals, and even by different professionals, to define bronchiolitis vary greatly (some authors restrict the diagnosis criteria to infants aged under 12 months, others also include successive episodes in the same patient).

Acute bronchiolitis places considerable demand on healthcare resources, not only in primary care, where it generates a significant number of consultations during both the acute and the sequelae phase, but also in hospitals, with major Accident & Emergency care requirements and a large number of admissions during epidemics. Of these cases, 5-16% will need to be admitted to a paediatric intensive care unit (PICU)[6]. In one study conducted in Spain in 2003, acute bronchiolitis was responsible for the hospitalisation of 37 per 1000 infants aged under 6 months, and 25 per 1000 infants aged under 12 months[7].

There is scientific disagreement as to how bronchiolitis should be handled, leading to major variation in how it is treated by different hospitals and healthcare professionals[1,4]. Many treatments which have not been proven to be effective are often used indiscriminately. Different styles in normal clinical practice may lead to variations not only in the consumption of medical resources but also in the clinical outcomes achieved, quality of healthcare and fairness of access and use of services[8,9].

For these reasons (high prevalence, confusion as to the definition of the illness, diversity of diagnosis criteria, variations in clinical practice and huge impact on consumption of medical resources), acute bronchiolitis has been selected as an entity for a CPG.

2. Scope and Aims

2.1. Scope

Patients with acute bronchiolitis are the target population of this guideline. The working group (WG) establishes the following functional definition of acute bronchiolitis, by consensus: *first episode of inflammation of the lower respiratory tract (bronchi and bronchioles), presumably virus-induced, in children aged under 24 months*.

The potential users of the CPG are all healthcare professionals involved in caring for patients diagnosed with acute bronchiolitis.

The CPG also brings together relevant information for carers (parents, guardians or others such as care home or nursery school staff looking after patients with acute bronchiolitis), particularly in sections which refer to measures to prevent transmission of the illness, supportive treatment and the warning signs of unfavourable progression.

The CPG includes recommendations for healthcare provided in Spain for patients with acute bronchiolitis in paediatric primary care centres, non-hospital-based paediatric appointments, paediatric hospitals and general hospitals that treat children.

The scope of this CPG does not include the treatment of late morbidity which may occur in patients with acute bronchiolitis, such as obliterative bronchiolitis, recurrent episodes of wheezing and asthma.

2.2. Aims

2.2.1. MAIN AIM

To develop an evidence-based CPG on acute bronchiolitis.

2.2.2. SPECIFIC GOALS

a) Establishment of a functional definition of acute bronchiolitis by the WG.

b) To define the risk factors for contracting the illness or for worse illness progression.

c) To define severity criteria.

d) To define criteria for referral from primary and outpatient care.

e) To define hospital admission and discharge criteria for Accident & Emergency and PICUs.

f) To provide support for healthcare professionals caring for patients with acute bronchiolitis.

g) To promote the rational use of diagnostic tests.

h) To promote the rational use of treatment resources.

i) To define and stimulate effective preventive measures.

j) To define guidelines to control hospital infection.

k) To establish appropriate monitoring guidelines for patients hospitalised for acute bronchiolitis.

l) To provide carers (whether relatives or not) with information that gives them a better understanding of the disorder affecting the child in their care.

m) To establish whether specific subsequent follow-up is needed for all or a subgroup of acute bronchiolitis patients.

3. Methods

The methods used are stated in the Methodology Manual for Developing CPGs of the Spanish Ministry for Health and Consumption[10].

The steps taken were as follows:

- Formation of a WG consisting of professionals who provide medical care at Barcelona's Sant Joan de Déu Hospital (emergency paediatricians, inpatient paediatricians and nursing staff), and a group of paediatricians who work at the national level. In order to incorporate the views of parents and carers, a group of parents were surveyed, and approved the information for patients.
- Formulation of clinical questions using the PICO (patient, intervention, comparison, outcome) method.
- Bibliographical search of PubMed/Medline, the Cochrane Library Plus in Spanish, CRD (Centre for Reviews and Dissemination, including DARE, NHS EED and the HTA da-tabase), the TRIP database, US National Guidelines Clearinghouse, UK National Library for Health, UK NICE Guidance, GuíaSalud (Spain), New Zealand Guide-lines Group, SIGN, ICSI, cmA Infobase (Canada) and ISI web of knowledge. Period covered: up to February 2009. Languages: there were no language restrictions, but most of the studies considered were in Spanish, English and French. The initial phase consisted of a preliminary search for CPGs and systematic reviews in the databases mentioned above. Seven CPGs on acute bronchiolitis were identified, with the illness understood to be a *first episode of inflammation of the lower respiratory tract (bronchi or bronchioles), presumably virus-induced, in children aged under 24 months*, which were evaluated using the AGREE instrument[11]. It was then decided to use four of these[1,2,4,12] (**Appendix 6**) as a secondary source of information. Thanks to their rigour and clarity they also provided inspiration and examples for some sections of this guideline, in line with the development/adaptation/updating method used in the asthma CPG of the Basque Country[13]. In the second phase, an extended search for original studies was carried out. Later on, search alerts were created in PudMed to identify relevant studies in the main biomedical journals.
- Quality evaluation of studies and summary of evidence for each question, following the recommendations of SIGN (the Scottish Intercollegiate Guidelines Network).
- Formulation of recommendations based on SIGN's «formal evaluation» or «reasoned judgement». Levels of evidence and grades of recommendations were assigned using SIGN's system (**Appendix 1**). Disputed recommendations or those not based on evidence were decided on by simple consensus of the WG.
- The methodology collaborators advised the WG and helped review the first draft of the guideline. External reviewers helped review the second draft. The various

scientific societies involved (the Spanish Paediatrics Association [AEP], the Spanish Society for Paediatric Respiratory Medicine [SENP], the Spanish Society for Neonatology [SEN], the Spanish Association for Paediatric Primary Care [AEPap], the Spanish Society for Outpatient Paediatrics and Primary Care [SEPEAP], the Spanish Society for Paediatric Intensive Care [SECIP], the Spanish Society for Paediatric Emergency Care [SEUP]) were contacted, and are also represented by members of the WG and external reviewers.

– Material detailing the information according to the CPG methodology process is available at www.guiasalud.es.

4. Diagnosis

4.1. Clinical Severity Criteria and Risk Factors

Questions to Answer

- In patients with acute bronchiolitis, what clinical severity criteria can be considered for the progression of bronchiolitis?

CPGs[1,2,4,12] consider the following clinical severity criteria: **tachypnoea and cyanosis, age under 12 weeks and refusal to feed (intake less than 50%), lethargy, history of apnoea, nasal flaring, grunting and severe retractions** (grade A, NZGG[4]; grade B, AAP[1]; opinion of experts, SIGN). The upper airways should be unblocked before physical examination, as a patient whose upper airways are obstructed by mucus may present increased signs of respiratory difficulty.

A prospective study published in 2006 concluded that BR > 45 bpm, saturation < 95% and age < 6 months are objective, reproducible parameters that may be significant in predicting the need for hospital admission. They therefore indicate severity, which reaffirms CPGs' recommendation of considering tachypnoea, low oxygen saturation and young age to be severity criteria. — Descriptive, 3

Various CPGs[1,2,4,12] identify the following as factors associated with severe acute bronchiolitis: **comorbidities (heart disease, immunodeficiency, chronic lung disease, prematurity)** with grade B according to the AAP[1], **smoking around the child, more siblings, overcrowding and poverty** (grade C, SIGN[4]) and **recent symptom onset, understood as less than 72 hours** (expert opinion, NZGG[12]). — CPGs

In line with CPG recommendations, a study published in 2007[6] showed that the main risk factor for PICU admission was young age, and the main determining factors for severe progression in PICUs was the association of two or more risk factors (age under 6 weeks, prematurity < 37 weeks, chronic lung disease, heart disease, neurological disease, immunodeficiency or another chronic disease), consolidation on X-rays and history of apnoea on admission. Mortality due to bronchiolitis was low (associated with previous chronic diseases). — Descriptive, 3

Turning to **number of siblings and nursery school attendance**, only SIGN's CPG[4] asserts that the number of siblings and nursery school attendance have been associated with a higher risk of acute bronchiolitis

or RSV infection. More recent studies[15-18] have also linked siblings to a greater risk of acute bronchiolitis or RSV infections. Figueras Aloy, whose work[18] studies the risk factors for hospital admission due to RSV in children born after 33-35 weeks' gestation, found that having siblings and attending nursery school were risk factors.

CC, 2-
CH, 2+
CC, 2+

CPGs[1,2,4,12] do not address birthweight or maternal age as possible risk factors for acute bronchiolitis or greater severity. In a cohort study, Koehoorn[15] finds that children whose mothers are aged < 20 years and those with a low or very low birthweight (1500-2500 g [3.3-5.5 lb] and < 1500 g [< 3.3 lb] respectively) are at greater risk of acute bronchiolitis. Rossi[17] describes a higher rate of hospital admission due to syncytial respiratory virus (RSV) in children with low birthweight (< 2500 g).

CH, 2+
CC, 2-

Regarding the effects of **patients' chronological age at the beginning of the respiratory virus season**, according to SIGN's CPG[4] (grade C) very small infants (no chronological age is stated) have a greater risk of hospitalisation, and the NZGG's CPG[12] (expert opinion) states that patients referred should be less than 2 months old. The CCHMC's CPG[2] (grade C) says that those aged under 3 months have a greater risk of hospital admission and morbidity. Finally, the AAP's CPG[1] (grade B) asserts that the greatest risk of severe illness is recorded in patients aged under 6-12 weeks, adding that these patients suffer from apnoea more frequently, which also entails a higher risk of hospital admission, PICU admission and mechanical ventilation. Two studies[17,18] found that a younger age at the beginning of the RSV season was associated with a greater risk of hospital admission due to RSV. In the second of these, patients were born after 32-35 weeks' gestation, and the age associated with risk of hospital admission due to RSV is under 10 weeks.

CPG
CC, 2-;
CC, 2+

SIGN's CPG[4] does not conclude (grade C) that **atopy** is a risk factor for severity, as no such link has been demonstrated.

CPGs

All CPGs[1,4,12] agree on the protective value of **breastfeeding** (grade A, NZGG[12]; grade C, SIGN[4] and AAP[1]). Studies published later than CPGs provide information which is consistent with this statement. One of these[19] evaluated the nutritional status and type of feeding in relation to the severity of acute bronchiolitis, and found that patients who were breastfed for longer progressed better (less time receiving oxygen therapy and shorter hospital stays). However, no relationship was found between nutritional status and severity of acute bronchiolitis. Another study[20] examined the relationship between breastfeeding, exposure to tobacco and severity of acute bronchiolitis and found that the length of breastfeeding (whether alone or combined with bottle-feeding) was associated with better progression; that environmental exposure to tobacco smoke exacerbated symptoms and the worsened the prognosis of

CPGs
CH, 2-
Descriptive, 3

patients with bronchiolitis; and that breastfeeding seemed to have aprotective effect even in patients exposed to tobacco.

One study adds another risk factor to be considered for severe bronchiolitis[21]. This study examined the relationship between **exposure to pollution** (ozone, material particles ≥ 2.5 microns, carbon monoxide, sulphur dioxide) and severity of acute bronchiolitis. It found that chronic and subchronic exposure to material particles with diameter ≥ 2.5 microns was associated with an increased risk of hospital admission due to bronchiolitis.

CC, 2+

Bloemers[22] presents a study which finds that **Down's syndrome** is an independent risk factor for severe RSV infection.

CH, 2+

A multicentre study in patients with RSV infection[23] finds that **neuromuscular disease** results in a greater risk of PICU admission, mechanical ventilation and mortality, and therefore of severe illness.

CC, 2+

Some studies have attempted to relate the **various aetiological agents** of acute bronchiolitis with differing clinical progression. A study of patients admitted to PICUs for respiratory infections[24] found that the average age of patients with RSV infections was significantly lower than that of patients with other viral infections; that bronchiolitis was significantly associated with RSV; and that prematurity and chronic lung disease were associated only with RSV infection, not with other viral infections.

Descriptive, 3

Another study[25] of patients admitted to hospital for a viral infection of the lower airways (bronchiolitis or bronchopneumonia) found that RSV was associated with respiratory infections in younger patients and those with more severe progression, but that no subtype of RSV was associated with greater severity. It does not specify whether aetiological agent determined better or worse progression among those with bronchiolitis.

Descriptive, 3

Fodha et al.[26] examined the relationship between the **viral load in the nasopharynx, type of RSV (A or B)**, patients' characteristics and severity of bronchiolitis (in terms of BR, length of hospital stay, rate of PICU admission and rate of mechanical ventilation). Like other studies, it found that patients with gestational age < 37 weeks, birthweight < 2,500 g [5.5 lb] and chronological age < 28 days presented greater severity. They also found a positive relationship between viral load and severity. No association was found between subgroup of RSV and severity.

Descriptive, 3

The severity of bronchiolitis probably depends not only on factors connected with the virus itself (type, subgroup, viral load, etc.), but also on factors relating to the host. For example, one study[27] found that some **polymorphisms of interleukin-8 (IL-8)** (which regulates Th2/Th1 balance) were associated with greater severity. Although they are of little practical value for clinical practice, these studies are important, as they provide more information on the aetiopathology of bronchiolitis and so that new treatments can be developed.

CC, 2-

Recommendations

A	The following are considered to be clinical severity criteria for the progression of bronchiolitis: • Refusal to feed or digestive intolerance, • Lethargy, • History of apnoea, • Tachypnoea for the patient's age, • Nasal flaring, severe retractions, grunting and cyanosis.
B	The following are considered to be risk factors for severe progression of bronchiolitis: • Age under 12 weeks, • The following comorbidities: haemodynamically significant heart disease, immunodeficiency, chronic lung disease, prematurity;
C	• Rapid progression (< 72 hrs), • Smoking around the child, • More siblings and nursery school attendance, • Overcrowding and poverty, • No breastfeeding, • Down's syndrome, • Neuromuscular disease;
D	• Low birthweight (< 2,500 g [5.5 lb]), • Young mother, • Younger age at the beginning of the RSV season.
D	There is insufficient evidence to conclude whether or not the following are risk factors for severity: • Any specific aetiological agent, • Any specific type of RSV (A or B), • High RSV viral load in the upper nasopharynx, • Some genetic polymorphisms.
C	Atopy has not been shown to be a risk factor for severity.
√	The upper airways should be unblocked before the severity of a patient's condition is assessed.

4.2. Severity Scales

Questions to Answer

- In patients with acute bronchiolitis, are assessment scales useful in taking decisions? What scales should be used?

There is insufficient evidence on the use of scales for acute bronchiolitis. Also, there are no validated scales specifically for acute bronchiolitis. The fact that several different scales have been used in work on bronchiolitis treatment makes comparison difficult.

The NZGG's CPG[12] (expert opinion) proposes a scale which has not been validated. — CPG

Liu[28] proposes a clinical scale based on BR, retractions, dyspnoea and auscultation (total score between 1 and 12), compares intraobserver concordance between different healthcare professionals and finds good kappa indices. This study does not assess the scale's ability to assess severity or prognosis. — Concordance study, 3

There is a (double-blind) RCT published in 2007[29] which proposes a computerised system to quantify wheezing and crepitation, as a non-invasive, objective way to evaluate pre-treatment and post-treatment changes in bronchiolitis. As this is an objective method, it would make it possible to draw more reliable comparisons between the different treatments tried for bronchiolitis. However, it evaluates only respiratory sounds, which are not necessarily directly correlated to severity of illness. It is probably more useful for research than for daily clinical practice. — RCT and concordance study, 1-, 3

Recommendations

√	Although there are as yet no validated scales for the purpose, ideally the severity of patients with acute bronchiolitis should be assessed uniformly, using a scale.
√	The airways should be unblocked before the severity of a patient's condition is assessed.

4.3. Criteria for Referral from Primary and Outpatient Care to Hospitals

Questions to Answer

- In patients with acute bronchiolitis, what criteria may be useful in deciding whether to refer patients from primary and outpatient care to hospitals?

There is little evidence on criteria for referral from outpatient care to hospitals for patients with acute bronchiolitis. CPGs which provide recommendations on this[4,12] base them on the experience of the WG. In fact, SIGN's guideline[4] is based on evidence described by the NZGG[12]. Nevertheless, there is consistency between these CPGs.

CPGs

Patients with the following symptoms should be referred to hospital: refusal to feed (intake < 50% of usual intake), dehydration, lethargy, history of apnoea, BR > 70 bpm, grunting, nasal flaring, severe retractions, cyanosis, oxygen saturation < 92-94%, severe illness according to the scale proposed, uncertain diagnosis. Comorbidities, history of prematurity (< 32-35 weeks' gestation), age under 2-3 months, time since symptom onset (there is a risk of deterioration in the first 72 hours), parents' ability to handle the child, geographical factors, transport difficulties and social factors must also be considered.

Parents should be provided with information on how to handle acute bronchiolitis and grounds for repeat consultation.

Recommendations

√	Patients with the following symptoms should be referred to hospital; • Refusal to feed or digestive intolerance (approximate intake less than 50% of usual intake), • Dehydration, • Lethargy, • History of apnoea, • Tachypnoea for the patient's age, • Moderate or severe respiratory difficulty (grunting, nasal flaring, retractions or cyanosis), • Oxygen saturation < 92-94% when breathing ambient air, • Severe illness according to the scale used, • Uncertain diagnosis.

√	The following factors should be taken into account when referring a patient to hospital: • Age (< 2-3 months), • Comorbidities, • Symptom onset < 72 hrs, due to risk of deterioration, • Socioeconomic status of the patient's environment, geographical factors, transport difficulties, • Parents' or carers' ability to assess the severity of the child's condition.

4.4. Hospital Admission Criteria

Questions to Answer

- In patients with acute bronchiolitis, what criteria may be useful in deciding whether patients need to be admitted to hospital?

There is little evidence on what criteria should be used to decide whether or not to admit patients with acute bronchiolitis to hospital. Most CPGs state clinical signs that suggest severity and provide recommendations on when to refer patients from outpatient care, but do not define clear admission criteria. However, patients who need to be referred to hospital are probably sent there to assess whether they need to be admitted. This is confirmed by the works cited below.

A study published by Mansbach et al. in 2008[30] examines the opposite case, i.e. when it is safe to discharge a patient with acute bronchiolitis who has been admitted to the Accident & Emergency ward. According to these authors, the following factors are associated with safe discharge home from hospital:

CH, 2+

- Age > 2 months,
- No history of intubation,
- History of eczema,
- BR < 45 bpm (in patients aged 0-1.9 months), < 43 bpm (2-5.9 months) or 40 bpm (6-23.9 months),
- Slight or no retractions,
- Initial saturation > 94%,
- Fewer salbutamol or adrenaline treatments in the first hour,
- Adequate food intake.

Thus it could be said that it is not safe to discharge patients who do not meet these criteria. The need for hospital admission of these patients and all those who meet referral criteria should be evaluated.

Lind[31] carried out a review of the scientific literature and found that clinical judgement is still the main criterion when deciding whether to admit children with bronchiolitis to hospital, and that no objective assessment can replace it. However, Lind concludes that tachypnoea and hypoxia are the measures with the greatest predictive value, although even these are not highly sensitive.

Review, 4

Another study[32] develops and validates a clinical model to predict hospital admission (sensitivity 91%, specificity 83%) on the basis of a retrospective review, and finds a gradual increase in the risk of hospital admission in patients with increased dehydration, respiratory difficulty and tachycardia (> 97th percentile); and a gradual reduction as age increased. The model predicts hospital admission for all patients less than 2 months old.

Descriptive, 3

In a retrospective study, Willwerth[33] found that 2.7% of patients suffer apnoea, and that it is associated with younger age, younger post-conception age, prematurity and apnoea proceeding consultation. Risk criteria: age < 1 month in those born full-term, post-conception age < 48 weeks in premature infants, apnoea; sensitivity 100%, specificity 64%, negative predictive value 100%.

CH, 2

Recommendations

√	Hospital admission is recommended for patients who meet the following criteria: • Age under 4-6 weeks, • Refusal to feed or digestive intolerance (approximate intake less than 50% of usual intake), • Dehydration, • Lethargy, • History of apnoea, • Tachypnoea for the patient's age, • Moderate or severe respiratory difficulty (grunting, nasal flaring, retractions or cyanosis), • Oxygen saturation < 92 when breathing ambient air, • Comorbidities: haemodynamically significant heart disease, pulmonary hypertension, neuromuscular disease, oxygen-depended lung disease, immunodeficiency, • Uncertain diagnosis.

√	The following factors should be considered when deciding whether to admit a patient to hospital: • Other comorbidities: heart disease, chronic lung disease, history of prematurity, Down's syndrome, • Symptom onset < 24-48 hrs, rapid progression of symptoms, • Socioeconomic status of the patient's environment, geographical factors, transport difficulties, • Parents' or carers' ability to evaluate the severity of the child's condition.

4.5. PICU Admission Criteria

Questions to Answer

- In patients with acute bronchiolitis who need to be admitted to hospital, what criteria may be useful in deciding whether they need to be admitted to PICUs?

There is little evidence on indications for PICU admission, and SIGN's CPG[4] is the only one which addresses the subject. Its recommendation is based on expert consensus. PICU admission is indicated if it proves impossible to maintain oxygen saturation > 92% despite increasing oxygen therapy, if there is a deterioration in the patient's respiratory status with signs of increasing respiratory distress or signs of exhaustion, and if the patient presents recurrent apnoea.	CPG
A study conducted in a Spanish PICU[6] found that the main risk factor for PICU admission was young age (< 6 weeks). Perhaps this factor should therefore be considered when deciding whether to admit a patient to a PICU.	Descriptive, 3

Recommendations

√	PICU admission is indicated if it proves impossible to maintain oxygen saturation despite increasing oxygen therapy, if there is a deterioration in the patient's respiratory status with signs of increasing respiratory distress or signs of exhaustion, and if the patient presents recurrent apnoea.

4.6. Discharge Criteria

Questions to Answer

- In patients with acute bronchiolitis, what criteria may be useful in deciding when to discharge patients from hospital?

There is little evidence on discharge from hospital or Accident & Emergency wards. Only a few CPGs make recommendations on this subject. SIGN's CPG[4] (expert opinion) recommends saturation > 94% with no additional oxygen, maintained for 8-12 hours' monitoring, including a period of sleep, and that food intake be more than 75% of the patient's usual food intake. The CCHMC's CPG[2] (Grade D) recommends discharging patients when the following criteria are met: CPGs

- BR < 70 bpm with no clinical evidence of increasing respiratory distress,
- Carers able to clean the airways,
- Patient breathing without additional oxygen or with stable doses of oxygen which can be continued at home,
- Sufficient food intake to avoid dehydration,
- Adequate family resources, confident parents who have been trained,
- Adequate follow-up (home visits if necessary, usual paediatrician informed and agrees patient can be discharged).

Only one article has been found on criteria for discharge from Accident & Emergency wards[30]. This concludes that the following are safe discharge criteria: CH, 2+

- Age > 2 months,
- No history of intubation,
- History of eczema,
- BR < 45 bpm (0-1.9 months), < 43 bpm (2-5.9 months), < 40 bpm (6-23.9 months),
- Slight or no retractions,
- Initial saturation > 94%,
- Fewer salbutamol or adrenalin treatments in the first hour,
- Adequate oral food intake.

Recommendations

√	Patients must be monitored for approximately 8-12 hrs after oxygen is withdrawn. This must include a period of sleep.
√	Discharge should be planned from admission onwards (agree discharge criteria with parents on admission).
√	Patients can be discharged when: • BR is appropriate for the patient's age, with no clinical evidence of increasing respiratory distress, • Saturation > 94% when breathing ambient air, • Adequate food intake, • Carers able to clean airways, • Resources in the environment are appropriate (parents/carers provided with accurate information on progression and grounds for repeat consultation, parents/carers consent to the discharge, suitable follow-up possible).

4.7. Aetiological Agents

Questions to Answer

- In patients with acute bronchiolitis, what are the aetiological agents?

Publications are consistent on the seasonal nature of acute bronchiolitis (winter: November-March) in temperate climates (grade D, SIGN[4]). They also agree that bronchiolitis is connected with viral infections, mainly RSV (grade B, CCHMC[2]; grade D, SIGN[4]), but also associated with other viruses (parainfluenza, adenovirus, influenza, metapneumovirus, rhinovirus, enterovirus, bocavirus) and *Mycoplasma pneumoniae*. Concurrent infections have also been described. — CPGs

The seasonal nature of RSV in temperate climates is confirmed by an epidemiological study[34] conducted in the USA, which found other patterns in other climates (constant activity with increases in summer and autumn in hot, wet climates; constant activity in cold climates). — Epidemiological study, 3

One study[35] concluded that patients with bronchiolitis associated with rhinovirus presented more wheezing, received more steroids and were hospitalised for less time. Another study[36] found that rhinovirus was the second-most common cause of lower respiratory tract infections after RSV, and that patients with rhinovirus infections were admitted to hospital earlier in the progression of their illness and seemed to present more severity. Jaques[37] also found that rhinovirus was the second-most common cause of bronchiolitis in winter, and the most common in spring. This study found no differences regarding the length of hospital stays between patients with RSV and those with rhinovirus. Kim[38] presents a study in paediatric patients with lower respiratory tract infections, and states that in the series metapneumovirus is the most frequently isolated virus, followed by RSV. Clinical presentation of patients with metapneumovirus was no different from that of those with other viruses. Children with concurrent infections showed no greater severity. Peaks of incidence were observed in autumn and spring (the study was conducted in Korea), the male/female ratio is 2:1 and 58% of those infected were less than 2 years old. In a Spanish study, Alonso[39] demonstrates a *circannual* rhythm of RSV infection, with a seasonal peak in autumn-winter. The beginning of the season is somewhat variable, but its duration is fairly uniform.

CH, 2+

Descriptive, 3

Descriptive, 3

Descriptive, 3

It is possible that progression and severity of bronchiolitis vary according to aetiology. However, more studies are required to provide more evidence of this.

Recommendations

B	Acute bronchiolitis is associated with viral respiratory infections.
C	To date it has been described in association with the following: RSV (main cause), rhinovirus, enterovirus, adenovirus, metapneumovirus, influenzas, parainfluenza, bocavirus. Concurrent viral infections have been described. An association with *Mycoplasma pneumoniae* has also been described.
D	Progression and severity may depend on aetiology, but to date there is insufficient evidence of this.
D	Healthcare professionals must bear in mind the time of year when making diagnoses. Spain, bronchiolitis has a seasonal peak (autumn and winter).

5. Additional Examinations

5.1. Blood Count, C-Reactive Protein (CRP), Procalcitonin (PCT) and/or Blood Cultures

Questions to Answer

- In patients with acute bronchiolitis, when are blood counts, C-reactive protein (CRP) assays, procalcitonin (PCT) assays and/or blood cultures needed?

CPGs[1,2,4] agree that routine additional examinations are not recommended for patients with typical acute bronchiolitis (grade A, CCHMC[2]; grade B, AAP[1]), because it is diagnosed clinically and because it presents a lower incidence of bacterial illnesses than patients with fever but without bronchiolitis. In particular, SIGN's CPG[4] recommends not performing blood counts in patients with typical acute bronchiolitis (grade D).	CPGs
One SR[40] states that there is little information available on how useful a white blood cell count is in acute bronchiolitis.	SR RCT, 1++
In two studies which examined the incidence of potentially serious bacterial infection in infants aged under 3 months with fever and with or without acute bronchiolitis[41,42], n = 3066 and 448 respectively, it was found that patients with bronchiolitis had a significantly lower incidence of potentially serious bacterial infections (in one of the studies, no patients in the bronchiolitis group had potentially serious bacterial infections; in the other, only 2.2% did, all of which were urinary infections, not sepsis).	CH, 2-
Purcell[43] presents a retrospective study of patients with RSV infections of the lower respiratory tract (n = 1,920) with or without fever in whom blood counts and bacterial cultures were performed, and compares white blood cell counts and positive cultures. Among those who had fever (n = 672), the positive culture rate was 5% (94% urinary infections). No statistically significant differences were found between the white blood cell counts and the positive culture rate. Only 3 cases of positive blood cultures were found, and only one of these was a positive blood culture with no urinary infection, in a infant girl aged 6 months with temperature 38.5 °C and WBC 38,200/µl.	Descriptive, 3

There is consistency between the studies, with low rates of bacterial infection found in bronchiolitis patients. When such infection is present, it is usually a urinary infection.

The only study[44] that evaluates how useful white blood cell counts are in bronchiolitis patients does not find them to be useful in predicting bacterial infection. — Descriptive, 3

No studies were found on the use of CRP and PCT assays in patients with bronchiolitis. In studies involving patients with fever but without bronchiolitis[44,45], CRP and PCT seem to be good markers of potentially serious bacterial infection. Of the two, PCT seems to be more accurate, particularly when fever progresses rapidly. — Descriptive, 3; CH, 2-

Recommendations

D	Routine blood counts, CRP assays and/or PCT assays are not recommended in patients with typical acute bronchiolitis.
D	Determining CRP and/or PCT levels may be useful in patients with acute bronchiolitis and fever in whom a potentially serious bacterial infection is suspected.
C	Routine blood bacteria tests are not indicated in children with typical acute bronchiolitis and no fever. Their use in patients with fever must be assessed on a case-by-case basis.

5.2. Sediment and/or Urine Culture

Questions to Answer

- In patients with acute bronchiolitis, when are urine tests and/or urine cultures needed?

CPGs CPGs[1,2,4] agree that routine additional examinations should not be recommended for patients with typical acute bronchiolitis, because it presents a lower incidence of bacterial illnesses than patients with fever but without bronchiolitis (grade A, CCHMC[2]; grade B, AAP[1]).

However, as it has been observed that infants aged under 60 days with acute bronchiolitis and fever have a significant incidence of urinary infections, SIGN's CPG[4] does recommend ruling out this possibility in this group of patients (grade C).

In two studies which examined the incidence of potentially serious bacterial infections in infants aged under 3 months with fever and with or without acute bronchiolitis[41,42], n = 3066 and 448 respectively, it was found that patients with bronchiolitis had a significantly lower incidence of potentially serious bacterial infections (in one of the studies, no patients in the bronchiolitis group had potentially serious bacterial infections; in the other, only 2.2% did, all of which were urinary infections, not sepsis).	CH, 2-
Purcell[43] presents a retrospective study of patients with RSV infections of the lower respiratory tract (n = 1,920) with or without fever in whom blood counts and bacterial cultures were performed, and compares white blood cell counts and positive cultures. Among those who had fever (n = 672), the positive culture rate was 5% (94% urinary infections). No statistically significant differences were found between the white blood cell counts and the positive culture rate. Only 3 cases of positive blood cultures were found, and only one of these was a positive blood culture with no urinary infection, in a infant girl aged 6 months with temperature 38.5 °C and WBC 38,200/μl.	Descriptive, 3
There is consistency between the studies, with low rates of bacterial infection found in bronchiolitis patients. When such infection is present, it is usually a urinary infection.	

Recommendations

C	Routine urine bacteria tests are not indicated in children with typical acute bronchiolitis and no fever. The possibility of a urinary infection must be considered in patients aged under 3 months with acute bronchiolitis and fever.

5.3. Blood Gas Tests

Questions to Answer

- In patients with acute bronchiolitis, when are blood gas tests needed and what type is required?

CPGs[2,4] are consistent in recommending that routine blood gas tests should not be performed in patients with bronchiolitis. They insist that diagnosis and determination of severity must be based on clinical criteria (expert opinion). SIGN's CPG[4] suggests that blood gas testing might have a role to play in assessing patients with severe respiratory difficulty or those with retractions who may be entering respiratory failure, and that knowing arterial CO_2 levels may indicate the need to transfer patients to PICUs (expert opinion). SIGN's[4] and the CCHMC's[2] guidelines mention arterial or capillary blood gas tests, but not venous tests. However, they do not recommend any specific type of blood gas test.	CPGs
No studies were found on how useful blood gas testing is or on the type of blood gas test to use in patients with acute bronchiolitis. In one study on the efficacy of continuous positive airway pressure (CPAP) with heliox vs. air/oxygen[46], CO_2 and SpO_2 levels were measured.	RCT, 1-

Recommendations

√	Routine blood gas tests (capillary or arterial) are not recommended for patients with acute bronchiolitis.
√	Blood gas tests (capillary or arterial) may have a role to play in the assessment of patients with severe respiratory difficulties who may be entering respiratory failure.
√	Determining transcutaneous oxygen saturation and CO_2 pressure may be useful in establishing the blood gas status of patients with acute bronchiolitis non-invasively.

5.4. Chest X-Rays

Questions to Answer

- In patients with acute bronchiolitis, when are chest X-rays needed?

No CPGs recommend routine chest X-rays for patients with acute bronchiolitis who present typical clinical progression and a mild-moderate process (grade B, AAP[1]; grade C, SIGN[4] and NZGG[12]), as although they show changes in many bronchiolitis patients, chest X-rays have not been shown to be effective in distinguishing between viral and bacterial processes or predicting severity. On the other hand, when they are performed the number of antibiotics and other treatments prescribed increases[1]. It is recommended that chest X-rays be reserved for patients with uncertain diagnoses (grade A, CCHMC[2]) or those with atypical clinical presentation (expert opinion, SIGN[4]), severe processes or poor progression (grade B, AAP[1]). — CPGs

An SR[40] draws the same conclusion. — SR RCT, 1++

No new studies which aim to examine the role of chest X-rays in patients with acute bronchiolitis have been identified. A retrospective descriptive study[6] found that consolidation on X-rays was associated with severe progression in PICUs, but the study design does not allow a causal relationship to be inferred. — Descriptive, 3

Recommendations

A	Routine chest X-rays are not recommended for patients with typical acute bronchiolitis.
B	Chest X-rays should be reserved for patients whose diagnoses are uncertain and those with atypical clinical presentation, severe processes or unfavourable progression.
C	Chest X-rays are not useful in distinguishing between bacterial and viral infections.
A	Chest X-rays increase the unnecessary use of antibiotics.

5.5. Virus Tests

Questions to Answer

- In patients with acute bronchiolitis, when do associated viruses need to be investigated?
- In patients with acute bronchiolitis in whom RSV infection is investigated, what laboratory technique should be used?

CPGs[1,4,12] mention that RSV tests are useful in establishing hospital cohorts when it is impossible to isolate patients in single rooms (grade B, AAP[1]; grade C, NZGG[12]; grade D, SIGN[4]), but they also all say that in other respects they have little effect on the diagnosis and treatment of these patients (grade B, AAP[1]; grade C, NZGG[12]).

CPGs and Bordley's systematic review[40] mainly deal with the identification of RSV, not other viruses, although they do mention that other viruses can cause acute bronchiolitis. — SR RCT, 1++

CCHMC's CPG[2] (grade A) and Bordley's review[40] suggest that in small infants a positive test may reduce the number of additional examinations needed. — CPG SR, 1++

Several recent studies address respiratory viruses and their role in various respiratory illnesses in children, as well as subsequent progression after the acute phase of the illness (2 CH studies[35,50] and 6 descriptive studies[24,37,38,47-49]). Progression and severity may depend on aetiology, but more studies are required to provide more evidence on this. These studies are heterogeneous, and it is difficult to establish the role played by each virus in acute bronchiolitis. To date it seems that determining aetiology is not of use in treating patients with acute bronchiolitis. — CH, 2+, 2- Descriptive, 3

CPGs contain little information on what technique should be used to determine RSV if necessary. Only SIGN's CPG[4] refers to this, and even it does not recommend any specific technique. It mentions that despite being less sensitive rapid tests have been shown to be acceptable when compared to laboratory tests, and they have the advantage that they can be performed wherever the patient is being cared for. SIGN's CPG[4] also says that rapid virus tests have been shown to be cost-effective, and that they reduce hospital stays, use of antibiotics and the number of microbial assays performed.

Two studies[51,52] and a review of the scientific literature[53] agree that molecular assays are more sensitive than rapid tests. Henrickson[53] mentions that thanks to molecular assays' high sensitivity and specificity they are replacing cell culture as the benchmark for diagnosis of viral infections. They are more expensive and somewhat slower than rapid tests (although much faster than cell cultures), and are not available at all hospitals. Tests based on antigen detection are usually available, and they are easy to use, give rapid results and are cheap; however, they are less sensitive and specific than other techniques.

Diagnostic test, 3

Review, 4

Recommendations

B	Routine virus tests are not recommended in the assessment of patients with acute bronchiolitis, as they do not affect their treatment.
A	RSV tests may be useful in establishing hospital cohorts when patients cannot be isolated.
√	Identifying respiratory viruses in patients with acute bronchiolitis may be of epidemiological interest.
D	To date, identifying other respiratory viruses does not appear to be useful in handling patients with acute bronchiolitis.
√	Ideally, all patients with acute bronchiolitis should be isolated. If this is not possible, cohorts should be established for all the viruses that can be identified.
D	If RSV identification is considered necessary to establish hospital cohorts and this occurs during an epidemic, rapid diagnostic tests may be used.
√	Molecular techniques may be useful for research studies or cases in which a patient's diagnosis is uncertain.

6. Treatment

6.1. Oxygen

Questions to Answer

- In patients with acute bronchiolitis, what is the arterial oxygen saturation threshold, measured via pulse oximetry, for administering oxygen?

CPGs[1,2,4,12] recommend giving additional oxygen to patients with saturation < 90-92%, but these recommendations are based on expert consensus, as no studies have been identified on the oxygen levels necessary in patients with acute bronchiolitis. The CCHMC's CPG[2] concludes that the normal range for oxygen saturation is variable and patient-specific, and recommends discontinuing oxygen therapy when haemoglobin saturation is > 94%. The AAP's CPG[1] also explains the reason for this variability: the haemoglobin dissociation curve is affected by various factors.

CPGs

No studies or reviews on the subject have been found.

Recommendations

√	A decision to administer oxygen must be based on assessment of both signs of respiratory difficulty and oxygen saturation measured by pulse oximetry.
√	Children with severe respiratory difficulty and/or cyanosis and/or SpO_2 < 92% must be given additional oxygen.
√	Consider withdrawing additional oxygen when SpO_2 remains steady at > 94% when breathing ambient air.
√	Oxygen should be prepared appropriately (warmed and humidified).

6.2. Bronchodilators

Questions to Answer

- In patients with acute bronchiolitis, are nebulised bronchodilators (salbuta-mol, terbutaline, adrenaline, ipratropium bromide, xanthines) beneficial?
- In patients with acute bronchiolitis, is there another useful route of administration for any bronchodilator?

There is a substantial amount of evidence on the benefits of bronchodilators in acute bronchiolitis, with consistent results.

All CPGs[1,2,4,12] and SRs[54,55] conclude that bronchodilators are not recommended for acute bronchiolitis treatment (grade A, NZGG[12] and CCHMC[2]; grade B, SIGN[4] and AAP[1]). This is because many studies have failed to demonstrate that they are effective, and in studies in which they have shown an effect it has been moderate and transitory (improvement in clinical scale or oxygen levels) and has not affected the overall progression of the illness or reduced hospital admission rates or lengths of hospital stays. Adrenalin appears to be somewhat superior to salbutamol and placebo, but only in non-hospitalised patients[55]. These publications also state that the potential side effects of these drugs and their costs must be assessed. The fact that beneficial effects have occasionally been shown justifies the recommendation given in two CPGs[1,2] of considering a therapeutic test with bronchodilators and discontinuing treatment if no improvement is shown (grade A, CCHMC[2]; grade B, AAP[1]).

CPGs
SRs
RCT, 1++

CPGs[4, 12] agree that anticholinergics should not be used for acute bronchiolitis (grade C, NZGG[12]; expert opinion, SIGN[4]).

CPGs

More recently, Levin[56] presents a controlled, blinded randomised clinical trial (RCT) in patients with acute bronchiolitis treated with mechanical ventilation, and finds a decrease in inspiratory peak flow both with adrenaline and with salbutamol and levosalbutamol, but of little clinical significance. This study finds a significant increase in HR as a side effect of these treatments. Another double-blind RCT29 found no differences between salbutamol and adrenalin, but did not compare these with a placebo.

RCT, 1-

RCT, 1-

CPGs[1,2,4,12] and SRs[54,55] examine the benefits of inhaled bronchodilators, but none of them refers to other routes of bronchodilator administration. With the exception of one old retrospective study[57] which studies the use of terbutaline in patients with bronchiolitis and finds no beneficial effect, no studies have been identified on the administration of oral xanthines or terbutaline, subcutaneous adrenaline, oral salbutamol or intravenous salbutamol.	Descriptive, 3
One study[58] reviews the scientific literature on the effects of xanthines on apnoea associated with acute bronchiolitis. It finds 3 studies with a total of 10 cases (one retrospective review of 7 cases, one description of 2 cases and a report of 1 clinical case), all ex-premature infants born at 29-36 weeks' gestation, who were administered caffeine, theophylline or aminophylline and all showed favourable responses. Sajit[59] presents another 3 cases of ex-premature infants who present apnoea in a bronchiolitis context, and who also improve after administration of caffeine.	Case series, 4

Recommendations

A	Routine ß$_2$-adrenergic agonist bronchodilating treatment is not recommended for acute bronchiolitis.
C	Nebulised ipratropium bromide is not recommended for the treatment of acute bronchiolitis.
A	Nebulised adrenaline is not recommended as routine treatment for acute bronchiolitis in children.
B	If a bronchodilator is considered necessary, therapeutic testing is recommended. Treatment should only be continued if there is a clinical response.
√	Xanthines, oral terbutaline, subcutaneous adrenaline, oral salbutamol and intravenous salbutamol are not recommended for patients with acute bronchiolitis.
D	Xanthines may be useful in treating apnoea associated with acute bronchiolitis in ex-premature infants.

6.3. Nebulised Hypertonic Solution and rhDNase

Questions to Answer

- In patients with acute bronchiolitis, is nebulised rhDNase, saline solution or hypertonic solution useful?

Quality studies which have examined the efficacy of rhDNase in patients with acute bronchiolitis[60,61] have not demonstrated that it is effective.	RCT, 1+, 1-
Only one study[62], with a short, heterogeneous series (5 cases), describes clinical improvement in connection with rhDNase.	Case series, 3
Studies which have examined the efficacy of 3% nebulised saline solution are consistent and are compiled in a Cochrane review[63], which demonstrates its efficacy in reducing the average length of hospital stay of patients with bronchiolitis (by approximately 1 day). It is the only treatment that has achieved this effect. No harmful side effects have been found.	SR RCT, 1++

Recommendations

A	3% nebulised saline solution in patients admitted to hospital with acute bronchiolitis, nebulised either alone or with bronchodilators and in repeated doses, is a useful treatment in reducing the length of hospitalisation. It is therefore recommended.
A	rhDNase is not recommended for patients with acute bronchiolitis.

6.4. Mucolytics, Antitussives, Nasal Decongestants, Alternative Therapies and Other Treatments Tested in Acute Bronchiolitis

Questions to Answer

- In patients with acute bronchiolitis, are mucolytics, antitussives and nasal decongestants useful in improving clinical presentation and progression?
- What other treatments have been tried in patients with acute bronchiolitis, and what have been the results?

There is little evidence on the benefits of mucolytics, antitussives or nasal decongestants for acute bronchiolitis. Only one CPG, that of the CCHMC[2] (grade B), mentions them. Its recommendation is not to use oral decongestants or nasal vasoconstrictors to treat acute bronchiolitis, although it does not refer directly to antitussives or mucolytics. This recommendation is based on the lack of evidence that these drugs are useful in reducing coughs or congestion in children with infections of the upper or lower respiratory tract, and therefore in acute bronchiolitis. It also suggests that some components of these drugs may harmful to human health. — CPG

One study[54] examines the benefits of nasal phenylephrine drops and concludes that they are not effective. — RCT, 1+

The FDA[65] advises the public not to administer this type of treatment to patients aged under 2 years (expert opinion).

The 3 CPGs[1,2,4] that address the subject of **antihistamines, steam and alternative therapies** all agree that there is no evidence on the effectiveness of antihistamines, steam or alternative therapies such as homoeopathy. The CCHMC's CPG[2] mentions (grade C) that antihistamines, decongestants and nasal vasoconstrictors have not been shown to be beneficial in children with upper respiratory tract infections, and says that they have demonstrated side effects, so their use cannot be recommended. Turning to alternative therapies, the AAP's CPG[1] (grade D) states that there is no evidence that they are effective but their use is very widespread. They are therefore not recommended for use by clinicians, but it is recommended that carers be asked about them and that their risks and benefits be known. The FDA[65] does not recommend the use of these treatments in children aged under 2 years. — CPGs

There is a Cochrane review[66] on the use of **surfactants** in patients with acute bronchiolitis. It concludes that there is insufficient evidence available, but that surfactant treatment in seriously ill newborns may reduce the length of hospitalisation and mechanical ventilation, and that no mortality or adverse effects have been recorded in connection with surfactants. — SR RCT, 1+

A double-blind RCT[67] examines the efficacy of **inhaled furosemide** for acute bronchiolitis and finds no significant short-term clinical effects or reduction in length of hospitalisation, duration of oxygen therapy or time until full enteral feeding is achieved. — RCT, 1-

Recommendations

B	Mucolytics, antitussives and nasal decongestants are not recommended for the treatment of acute bronchiolitis.

D	Antihistamines, oral decongestants, nasal vasoconstrictors, steam and alternative therapies such as homoeopathy are not recommended for patients with acute bronchiolitis.
A	There is insufficient evidence to recommend the use of surfactants.

6.5. Antibiotics

Questions to Answer

- In patients with acute bronchiolitis, are antibiotics useful in improving clinical presentation or progression?
- In patients with acute bronchiolitis with atelectasis and/or images of alveolar involvement, are antibiotics useful?

Both CPGs[1,2,4,12] and the SR[68] agree that antibiotics should not be used indiscriminately to treat acute bronchiolitis (grade B, AAP[1] and CCHMC[2]; grade C, NZGG[12]; expert opinion, SIGN[4]). Bronchiolitis is a viral illness, so antibiotics would not be indicated. Several publications mention that antibiotics should only be used if there is evidence of a concurrent bacterial infection, and that their use does not prevent complications.

CPGs

The subject is addressed individually for each of the following potential concurrent infections: potentially serious bacterial infection, or PSBI (sepsis, meningitis, urinary tract infection [UTI], pneumonia) in infants aged under 60 days, acute otitis media (AOM), pneumonia.

SR RCT, 1+

• The incidence of PSBIs is described as low in patients with fever and acute bronchiolitis and/or RSV infection. Where PSBIs do occur, the most common are UTIs[1,4]. Only infants aged under 28 days present infection rates similar to those with no RSV infection[1]. This would justify a study of UTIs in infants aged under 60 days and a study of fever in those aged under 28 days even if they do not present with acute bronchiolitis[6,7,9].

• The works referred to state that AOM can be caused by RSV itself, that it is very common in patients with acute bronchiolitis and that where it occurs bacteria are isolated in a substantial number of cultures of tympanocentesis fluid. Otitis should therefore be treated in the same way as if the patient did not present with bronchiolitis[1]. AOM in patients with acute bronchiolitis is stated not to affect clinical or analytical progression[1,2].

• The AAP's CPG[1] mentions that approximately 25% of patients admitted to hospital with bronchiolitis have atelectasis or infiltrates on chest X-rays, but that bacterial pneumonia in patients with acute bronchiolitis is uncommon.

Two trials[69,70] examine the use of macrolides in patients with acute bronchiolitis, with conflicting results. It is thought that the effect of macrolides may be due not to their antibacterial action but to two possible effects on the airways: an immunomodulating effect (cytokine changes), which would suppress bronchial hyperreactivity; and inhibition of cholinergic transmission, which would lead to relaxation of the smooth muscle of the airways. In Tahan's study[70], clarithromycin is administered for 3 weeks, and a reduction in the average length of hospital stay, average length of oxygen therapy and hospital readmission rate are found. In Kneyber's study[69], azithromycin is administered and no significant differences are found between the treatment and placebo groups.

RCTs, 1-, 1+

There is little evidence on the benefits of antibiotics in patients with acute bronchiolitis and atelectasis or alveolar involvement. Both CPGs[1,2,4,12] and the SR[68] agree that antibiotics should not be used indiscriminately to treat acute bronchiolitis, but only two CPGs[1,12] mention their benefits in patients with abnormal chest X-rays. The NZGG's guideline[12] mentions that in studies including patients with pneumonia antibiotics have not shown any benefit in patients with acute bronchiolitis, and that their use does not prevent pneumonia. The AAP's guideline[1] mentions that approximately 25% of patients admitted to hospital with bronchiolitis have atelectasis or infiltrates on chest X-rays, but that bacterial pneumonia in patients with acute bronchiolitis is uncommon.

CPG
SR RCT, 1+

Spurling's review[68] explains the work published by Field in 1966: 150 children with bronchiolitis with fine crepitant rales or pulmonary consolidation on chest X-rays were assigned antibiotics (ampicillin) or no antibiotics at random. In RSV-positive children no significant differences were found between the groups with and without antibiotics in terms of fever, pulmonary symptoms, length of hospital stay, otitis media or chest X-ray findings. However, the review also mention that children who require PICU admission, particularly those who require mechanical ventilation, may have a higher rate of concurrent bacterial infection, which would justify greater use of antibiotics.

SR RCT, 1+

Recommendations

A	Antibiotics should not be used as routine treatment for acute bronchiolitis.
B	There is insufficient evidence on the value of macrolides in acute bronchiolitis. Their use is not recommended.
B	When there is a bacterial infection (e.g. a urinary infection or acute otitis media), this must be treated as it would be if the patient did not have bronchiolitis.
D	In patients with severe acute bronchiolitis requiring mechanical ventilation, a significant percentage have a concurrent bacterial lung infection. The use of antibiotics in these patients should be considered.
B	Antibiotics should not be used as routine treatment for bronchiolitis patients with atelectasis or alveolar involvement.
√	Antibiotics should be considered for patients with acute bronchiolitis who present clinical signs of severity and/or blood count, CRP and/or PCT alterations.

6.6. Heliox

Questions to Answer

- In patients with acute bronchiolitis, is a helium/oxygen gas mixture useful in improving clinical presentation or progression?
- In patients with acute bronchiolitis, is a mixture of helium and oxygen, rather than air and oxygen, pure air or pure oxygen, useful as a drug nebulisation medium to improve distal drug availability or response to the drug?

There are few studies on the benefits of heliox (a helium/oxygen gas mixture) for acute bronchiolitis. The studies yield conflicting results on clinical improvement, although they all agree that there are no adverse effects. Blinding is difficult because heliox affects patients' voices.

A study conducted in a PICU, in which facemask administration of heliox was studied[71], found a significantly shorter average PICU stay in the heliox group. The benefits of heliox are also described in another study, both administered through a facemask and given using nasal prongs[72], although this study includes patients with other disorders and finds a smaller beneficial effect in patients with bronchiolitis.

CH, 2-

Descriptive, 3

Combined use of heliox and CPAP[46] also shows improved clinical severity scale scores and reduced CO_2 levels measured using a transcutaneous sensor. This study is the only one to show reduced CO_2 levels and increased arterial oxygen saturation. This occurs in both treatment groups, although more markedly in the group treated with heliox. Two other studies[73,74] determine a beneficial effect of CPAP.

In contrast, another study[75] compared the need for non-invasive ventilation in one group given heliox and another treated with air/oxygen, both in a hood chamber, and found no significant differences in progression.

Descriptive, 3
RCT, 1-
RCTs, 2-

More studies are required on the benefits and cost-effectiveness of heliox.

Descriptive, 3

There is little evidence on the usefulness of heliox as a nebulisation medium, particularly in patients with acute bronchiolitis, but the studies there are describe benefits. Studies by Graner[76] and Hess[77] use a model of an intubated child's lung and compare the distribution of salbutamol with the heliox or nitric. The results show better distribution for heliox, particularly at a proportion of 70:30.

In a study of asthmatic patients[78], those who received heliox as a salbutamol nebulisation medium showed greater improvements in scores on the clinical severity scale used, and improved more quickly (statistically significant differences). Also, more patients in the heliox group were discharged from hospital (10/15 vs. 5/15), with no statistical significance. It is not known whether the improvement was due to better distribution of salbutamol or the direct effect of heliox itself.

Descriptive, 3

Recommendations

D	Heliox may be useful in patients with moderate to severe bronchiolitis, but more studies confirming this are needed.
√	Heliox as a drug nebulisation medium may improve the quantity of the drug that penetrates distally and drug distribution, but there are no specific studies involving patients with acute bronchiolitis.

6.7. Glucocorticoids

Questions to Answer

- In patients with acute bronchiolitis, is glucocorticoid treatment safe and effective in improving clinical presentation and progression?
- In patients with acute bronchiolitis who have required tracheal intubation, are glucocorticoids useful in reducing intubation time?

All the CPGs[1,2,4,12] and SRs[79,80] identified agree that no effect has been found for glucocorticoids via any route of administration (grade A, SIGN[4] and CCHMC[2]; grade B, AAP[1]; grade C, NZGG[12]), either in the acute phase of the illness or in preventing subsequent recurrent wheezing.	CPGs SRs RCT, 1++
One large-scale (n = 598) double-blind, multicentre RCT[81] (data were gathered at 20 sites) which compared a single dose of oral dexamethasone with a placebo also failed to find any significant differences in the need for hospital admission, RDACS (RDAI plus BR) scale scores, isolated BR, length of hospital stay or the need for hospital admission in the following 7 days.	RCT, 1+
Studies have appeared recently on patient progression according to which virus causes bronchiolitis. Until now this had not been studied separately. This might explain the differences observed in some studies mentioned in CPGs[2,12] which do describe some effect of steroids. This effect is diluted when combined with other studies, many of which are in RSV-positive patients. In this regard, Lehtinen[82] finds that patients with rhinovirus present more recurrent wheezing, and that the use of prednisolone in these patients reduces the number of these recurrent episodes, an effect not observed in RSV-positive patients. Mansbach[35] also reports that in his study children with rhinovirus head a greater incidence of a history of wheezing and received more steroids.	Descriptive, 3 CH, 2+
Plint[83] presents a double-blind multicentre RCT with a large number of patients. The trial had four treatment arms (two nebulised doses in Accident & Emergency plus a single oral dose daily for 6 days, begun in Accident & Emergency): adrenalin/dexamethasone, placebo/dexamethasone, adrenalin/placebo, placebo/placebo. A lower hospital admission rate was found in patients in the adrenalin/dexamethasone arm, although this relationship loses its statistical significance in analysis adjusted for multiple comparisons, and no effect is found in the other treatment arms.	RCT, 1+

Neither CPGs[1,2,4,12] nor SRs[79,80] directly address the benefits of glucocorticoids in intubated patients. Studies in this subtype of patient are not included in the bibliography for these documents, in which it is concluded that steroids are not beneficial.

Few studies have been found on the benefits of glucocorticoids in intubated, mechanically ventilated patients with acute bronchiolitis. One of the few there are[84] finds no significant differences regarding the duration of mechanical ventilation, stay at PICUs or total hospital stay. However, this study was designed to find differences in the amount of virus in secretions, and in order to detect significance regarding the duration of clinical parameters the difference would have needed to be above 50%. Another study which was designed to find clinical changes in this type of patient[85] found no significant differences in the duration of intubation, stay at PICUs, total hospital stay or oxygen therapy in the group studied as a whole; only if the groups were subsequently subdivided (less severity: less need for oxygen and lower average pressure; and greater severity, referred to as the bronchiolitis group and the pneumonia group respectively) was a significantly shorter duration of mechanical ventilation found in the bronchiolitis subgroup (-4.3 days; 4.9 vs. 9.2 days) in the group treated with dexamethasone.

RCT, 1-

RCT, 1-

Steroids were not shown to be effective in the group of children with acute bronchiolitis as a whole, and although there is little evidence there also seems to be no an effect in the subgroup of mechanically ventilated patients (with the exception of a very select group, and in a study with methodological weaknesses). For the present it therefore seems that steroids should not be recommended for these patients.

Recommendations

A	Glucocorticoids are not recommended for the treatment of acute bronchiolitis, in any dosage form.
B	Routine use of glucocorticoids is not recommended for patients with acute bronchiolitis who are being mechanically ventilated.

6.8. Antivirals

Questions to Answer

- In patients with acute bronchiolitis, are antivirals useful in preventing contagion or improving clinical presentation or progression?

Only two CPGs[1,4] (grade B) and one Cochrane review[86] address the efficacy of ribavirin in treating bronchiolitis caused by RSV. They all agree that its use should not be recommended. SIGN's CPG[4], the bibliography of which includes the Cochrane review, finds two types of study of ribavirin, some assessing its effect during the acute phase of the illness and others evaluating its long-term effects. Among those which assess short-term effects, one shows a benefit. However, this study uses water rather than saline solution as a placebo, which may have harmful effects in patients who receive it and thus appear to show a benefit for ribavirin. If this study is excluded, the others found no effect for ribavirin. Long-term studies have also failed to find a beneficial effect.

CPGs

SR RCT, 1+

The AAP's CPG[1] (grade B) agrees that studies on the long-term effects of ribavirin do not show any beneficial effects. It also says that the studies are of poor quality. It finds 11 studies which assess the effects during the acute phase, all in small numbers of patients, 7 of which find a beneficial effect. However, this effect is only measured objectively, for example using oxygen levels or length of hospital stay, in 4 of the studies. If the potential risks of ribavirin for carers and its cost are taken into account, on balance it is not found to be beneficial. However, this CPG leaves the door open for its use in selected cases of patients with severe acute bronchiolitis caused by RSV or who are at risk of developing severe illness (patients with immunodeficiencies or haemodynamically significant cardiorespiratory disorders).

CPG

There is no mention of the use of ribavirin to prevent contagion.

There are two recent studies on ribavirin. One of these is a long-term follow-up study[87] which finds a decrease in the rate of recurrent wheezing and allergic sensitisation 6 years after receiving ribavirin for acute bronchiolitis caused by RSV. This study has major methodological shortcomings: the patients receiving ribavirin are different from those who do not, as they meet the administration criteria established by the hospital where the study was conducted. The other study[88] deals with patients with an underlying disorder, rather than bronchiolitis, who receive intravenous palivizumab for RSV infections. In addition, rather than assessing the effectiveness of ribavirin it simply states that 80% of those who received intravenous palivizumab also received ribavirin (22 nebulised, 3 intravenously), and describes the progression of all patients. They present a high survival rate, but it is difficult to establish the roles played by palivizumab and ribavirin in this.

CH, 2-

Descriptive 3

Recommendations

B	Ribavirin is not recommended for patients with acute bronchiolitis.
√	Ribavirin may have a role to play in severely immunocompromised patients with RSV infection.

6.9. Montelukast

Questions to Answer

- In patients with acute bronchiolitis, does montelukast improve clinical presentation or progression?

Only two of the CPGs[4,12] selected address this subject, and both are based on a single study on the efficacy of montelukast in acute bronchiolitis[89]. This study included patients aged 3-36 months who had been admitted to hospital for acute bronchiolitis and who were given montelukast every day for 28 days (beginning during the first 7 days of clinical presentation). A significant increase in the number of symptom-free days was found over a period of 56 days, as was a decrease in the time with a daytime cough. SIGN's guideline[4] mentions that the average age of children with acute bronchiolitis is less than that of the study (which means that its results cannot be applied generally), while the NZGG's guideline[12] says that the treatment is difficult to administer as it is in the form of chewable tablets, the only dosage form available in Spain when the guideline was compiled. Both agree that there is insufficient evidence on which to base recommendations on this subject.

CPGs
RCT, 1+

Bisgaard[90] himself has recently submitted a study similar to the one above, but with opposite results. This was a multicentre randomised clinical trial with a higher number of patients (n = 979) who were given montelukast (4 mg/day vs. 8 mg/day vs. placebo) for two periods (4 weeks and 20 weeks respectively) from symptom onset onwards. No significant differences were found[7] in terms of the number of days with no daytime or night-time symptoms, days with a cough, recurrent wheezing, use of bronchodilators, use of steroids or medical appointments with any of the administration guidelines. Another double-blind RCT[91] involving montelukast and a placebo administered during hospitalisation also failed to find any significant differences in length of hospital stay, scores on the clinical scale used or cytokine levels in nasal aspirate.

RCT, 1+

RCT, 1+

Recommendations

B	Montelukast treatment is not recommended for patients with acute bronchiolitis.

6.10. Supportive Treatment, Hydration and Nutrition

Questions to Answer

- In patients with acute bronchiolitis, are aspiration of secretions, humidification and positional measures useful in improving clinical presentation or progression?
- In patients with acute bronchiolitis, does breaking up feeds, thickening feeds, tube feeding or giving nil by mouth and hydrating intravenously improve clinical presentation or progression?

CPGs

Only two CPGs[2,4] address the subject of the benefits of aspiration of respiratory secretions in acute bronchiolitis (grade D, SIGN[4] and CCHMC[2]). The guidelines of the CCHMC[2] (grade D) and NZGG[12] (expert opinion) recommend using nasal drops of saline solution before feeding and before aspirating secretions.

Neither of these CPGs examines the effects of humidification or positional measures. The NZGG's CPG[12] does recommend minimal handling of patients with acute bronchiolitis, though with no prior reasoning (expert opinion).

Both CPGs[2,4] which cover the subject recommend aspiration of secretions on the basis that this in itself may improve the clinical presentation of patients with acute bronchiolitis, particularly if there is nasal obstruction. One of them also states that this may improve the efficacy of inhaled treatments, and says that nasal drops of saline solution can be used before aspiration. Both these CPGs base their recommendation on expert consensus, as there are no studies on the subject.

We were unable to find any SRs on this subject.

CPGs

There is no evidence on whether breaking up feeds, thickening feeds, tube feeding or giving nil by mouth and hydrating intravenously improves the clinical presentation or progression of patients with acute bronchiolitis. CPGs[1,2,4,12] provide recommendations based on expert opinion. They agree that patients with acute bronchiolitis are at risk of dehydration (due to feeding difficulties secondary to respiratory effort). It is therefore recommended that this issue be assessed and the patient be hydrated if required, although there is no information on whether intravenous hydration, continuous enteral hydration via nasogastric tube or occasional enteral hydration via nasogastric tube is best. Two of the CPGs[4,12] also recommend breaking up feeds (smaller, more frequent feeds). Thickening feeds is not mentioned. The AAP's CPG[1] mentions that these patients have an increased risk of pulmonary aspiration. The AAP's CPG[1] also mentions that inappropriate antidiuretic hormone secretion has been described in patients with acute bronchiolitis.

One study[92] examining deglutition via videofluoros-copy in patients with acute bronchiolitis was identified. 15 patients were studied, and 9 were found to have deglutition disorders (3 laryngeal aspirations, 2 tracheal aspirations, 4 bronchopulmonary aspirations). After the barium administered as videofluoros-copy contrast was thickened with rice cereals, the 3 laryngeal aspirations, the 2 tracheal aspirations and 3 of the 4 bronchopulmonary aspirations were corrected.	Case series, 3

Recommendations

√	Respiratory secretions should be aspirated before feeds, before each inhaled treatment and when signs of obstruction of the upper airways are detected (audible evidence of secretions, increased distress).
√	Saline solution drops may be used before secretions are aspirated.
√	Respiratory secretions should be aspirated before the severity of a patient's condition is assessed.
√	Humidification has not been shown to be useful in patients with acute bronchiolitis. It is therefore not recommended.
√	Positional measures (lifting the head of the cot) are recommended for patients with acute bronchiolitis.
D	The hydration and ability to take liquids of patients with acute bronchiolitis must be assessed.
D	Feeds should be broken up and/or thickened if feeding difficulties are detected.
D	Feeding via nasogastric tube may be an option for children at risk of dehydration or with progressive respiratory difficulties.
√	In children whose condition is most severe, particularly those whose illness progression may require endotracheal intubation, intravenous hydration is recommended.
D	Patients with acute bronchiolitis may present the syndrome of inappropriate antidiuretic hormone secretion.

6.11. Respiratory Physiotherapy

Questions to Answer

- In patients with acute bronchiolitis, is respiratory physiotherapy useful in improving clinical presentation or progression?

All three CPGs[1,2,4] and the Cochrane SR[93] conclude that **vibration or percussion** physiotherapy in patients with acute bronchiolitis does not have a beneficial effect in terms of clinical score, oxygen saturation or length of hospital stay (grade A, SIGN[4] and CCHMC[2]; grade B, AAP[1]). The CPGs are based on the same RCTs which are included in the Cochrane review for its recommendation. The only evidence therefore comes from these three studies.

CPGs

SR RCT, 1++

Another study[94] shows improved oxygen saturation, HR and clinical severity scale score after **slow prolonged exhalation and induced cough** physiotherapy. However, this study has major shortcomings: it examines only a few patients and has no control group; the average age of the patients included in the study (7 months) is unusual for work on bronchiolitis; their condition was mild (pretreatment severity scale score approximately 4/9, pretreatment $SpO_2 > 95\%$); it does not assess the effect on hospital admission or duration of hospital stays; and it includes patients with a history of "bronchiolitis", which means that these could have been cases of bronchospasm rather than bronchiolitis.

Descriptive, 3

Recommendations

A	Respiratory physiotherapy is not recommended for patients with acute bronchiolitis.

6.12. Non-Invasive Ventilation and Conventional Ventilation

Questions to Answer

- In patients with acute bronchitis who require hospitalisation, are non-invasive ventilation in the form of CPAP (continuous positive airway pressure) or other methods useful in improving clinical presentation and progression?
- In patients with acute bronchiolitis, when is conventional mechanical ventilation indicated?

SIGN's CPG[4] is the only one to cover the subject of mechanical ventilation in children with acute bronchiolitis. No distinction is made between non-invasive ventilation (in any form) and invasive ventilation (tracheal intubation), and it finds no evidence on the use of either. It provides a recommendation based on expert opinion, which suggests that children with severe distress should be transferred early, and that early ventilation of these patients and those with apnoea should be considered.

CPG

No SRs which covered this subject were found.

All studies which address the benefits of non-invasive ventilation in acute bronchiolitis find positive effects[73], and do not describe any problems with treatment tolerance or find any major side effects (the only side effects described were nasal lesions due to the application of nasal CPAP[95,96] and one pneumothorax which did not require drainage[96]).

Martinón-Torres[46] presents a study of children aged 2-24 months admitted to PICUs for acute bronchiolitis who received CPAP with heliox or air/oxygen. Decreased CO_2 measured transcutaneously and improved clinical scale scores were observed in both groups (they were more pronounced in the heliox group). None of the patients required intubation. — Descriptive, 3

Thia[97] presents a crossover RCT in which patients received 12 hours of CPAP or 12 hours of standard treatment (saline drip, oxygen therapy and minimal handling), followed by 12 hours of the other treatment. A significant decrease in pCO_2 was found after CPAP treatment, but this was greater in those who received it first. Another study in a PICU in patients aged under 3 months with acute bronchiolitis caused by RSV[74] describes an improvement in clinical scale scores and decreased effort of accessory muscles after CPAP (6 cm H_2O). None of the patients required intubation. — RCT, 1-

RCT, 1+

In a descriptive study, Mayordomo-Colunga[96] finds a success rate of 83% in patients treated with NIV (17 of them with CPAP). Failure is associated with apnoea, lower weight, younger age and less decrease in HR and BR. — Descriptive, 3

Campion[98] presents a study involving children with an average age of 49 days admitted to PICUs for RSV infections. Patients who received non-invasive ventilation (n = 69) show a decrease in pCO_2 and pH. 17% require intubation. The factors associated with failed non-invasive ventilation are apnoea, high pCO_2 on admission and a high score on the PRISM severity scale. — Descriptive, 3

Larrar[95] provides similar results in patients aged 2-24 months with acute bronchiolitis in whom decreased pCO_2 and BR were observed when nasal CPAP was applied, with an intubation rate between 22% and 27%, associated with higher PRISM scale scores and no decrease in CO_2 levels when CPAP was applied. This study also described shorter duration of respiratory support and PICU stays than in those receiving mechanical ventilation, although this may be because the latter presented greater severity. — Descriptive, 3

No studies which aimed to assess when mechanical ventilation should be administered to patients with acute bronchiolitis or which compared the benefits of different types of ventilation in these patients were found.

In the material and methods section of a study on the benefits of bronchodilators in ventilated patients, Levin[56] states the type of ventilation used in the study protocol: volume-controlled mechanical ventilation (Servo 300, Siemens). The guideline established is a tidal volume of 6-8 ml/kg and an expiratory pressure of 3-4 cm H_2O, and BR, inspiratory time and inspiration:expiration ratio (minimum 1:2) are adjusted to achieve arterial CO_2 pressures of 35-45 mmHg. An FiO_2 is administered to maintain SpO_2 at 90-95%. RCT, 1-

A retrospective study on HFOV in patients with acute bronchiolitis with hypercapnic respiratory insufficiency[99] found that after patients had been transferred from conventional mechanical ventilation to HFOV there was a decrease in MAP and FiO_2 administered and a decrease in partial CO_2 pressure in arterial blood. Descripive, 3

Recommendations

B	CPAP non-invasive ventilation is effective in patients with acute bronchiolitis who present severe respiratory difficulties, hypercapnia or recurrent apnoea.
B	CPAP non-invasive ventilation has few side effects and is well tolerated.
√	Non-invasive ventilation must be considered for acute bronchiolitis patients with respiratory insufficiency despite medical treatment.
√	Mechanical ventilation must be considered for acute bronchiolitis patients with respiratory insufficiency, those with apnoea, those in whom other measures, such as non-invasive ventilation (NIV), have failed and those with signs of imminent arrest.
√	HFOV appears to be useful in patients with hypercapnic respiratory insufficiency despite conventional mechanical ventilation.

7. Monitoring

7.1. Pulse Oximetry

Questions to Answer

- In patients with acute bronchiolitis, when is continuous or occasional oxygen saturation monitoring via pulse oximetry indicated?

SIGN's CPG[4] recommends monitoring haemoglobin saturation in all patients who attend hospital, as one study demonstrated that clinical evaluation was insufficient to assess oxygenation in children with respiratory disorders (grade C). The NZGG's CPG[12] (grade C) states that measuring oxygen levels (no method is specified) provides additional information and should be performed, as low oxygen levels are associated with greater severity, although it also states that low oxygen levels have been associated with greater use of additional examinations and treatments, and that one study showed that knowing oxygen levels prolonged hospital stays. For these reasons (increased number of examinations and treatments, longer hospital stays), and because some studies show that transitory low saturations can occur in healthy children, the guidelines of the AAP[1] and the CCHMC[2] (both grade D) recommend monitoring saturation but not continuously (the AAP[1] recommends intermittent measuring, particularly during remission, with grade D). The AAP's CPG[1] recommends (grade B) more frequent monitoring in patients with underlying disorders, because of their greater risk of severity.

CPGs

A retrospective study[100] found that the percentage of children requiring oxygen 6 hours after admission was higher than the percentage requiring oxygen on admission. This is attributed to the fact that continuous monitoring makes it more likely that low saturations will be detected at some point, leading to oxygen administration. Also, a strong correlation was found between the duration of oxygen therapy and length of hospital stays. The average length of hospital stays from resolution of all other problems to withdrawal of oxygen therapy is 66 hours.

Descripive, 3

Recommendations

C	Oxygen saturation should be determined via pulse oximetry (SpO_2) during initial examination of patients with acute bronchiolitis.
D	When a child's clinical presentation improves, it is no longer necessary to monitor SpO_2 continuously.
B	Children with high-risk comorbidities (clinically significant congenital heart disease, pulmonary hypertension, neuromuscular disease, oxygen-dependent lung disease and immunodeficiency) require more monitoring when their oxygen is being withdrawn.

7.2. CO_2 Monitoring

Questions to Answer

- In patients with acute bronchiolitis, when is continuous or occasional CO_2 monitoring (transcutaneous or exhaled) indicated?

No CPGs insist on the need to monitor CO_2 levels in patients with acute bronchiolitis. No SRs or articles providing evidence on this have been found.

One old descriptive article[101] states an average hypercapnia of 82 mmHg prior to intubation in patients who had required mechanical ventilation. This confirms that the respiratory insufficiency of patients with acute bronchiolitis is both hypoxaemic and hypercapnic. In fact, work on the use of CPAP for acute bronchiolitis to assess improvement uses CO_2 levels, among other parameters. Different studies use different systems to measure CO_2 levels, including transcutaneous sensors, capillary samples and arterial samples[46,95,97,98]. Descripive, 3

Recommendations

√	It may be useful to determine the CO_2 levels of patients with moderate or severe acute bronchiolitis non-invasively, particularly in patients receiving ventilatory support.

7.3. Heart Rate, Breathing Rate, Severity Scale

Questions to Answer

- In patients with acute bronchiolitis, when is monitoring of BR, HR and a clinical severity scale indicated?

CPGs

Only the CCHMC's CPG[2] provides explicit recommendations on monitoring clinical scale scores, HR and BR. It recommends monitoring HR and BR particularly during the acute phase of the illness (grade B), arguing that this is when there is the greatest risk of apnoea and bradycardia. It recommends repeat clinical assessments (although the use of a clinical scale is not mentioned) as the main tool to detect deterioration in patients (grade D). SIGN's CPG[4] makes no mention of monitoring these clinical signs, but does say that a BR above 70 bpm is a sign of severity. The NZGG's CPG[12] provides its own clinical scale, but does so in the section on assessment of severity, and it does not mention repeated use of this to monitor patients or refer to monitoring HR and BR to assess progression.

Recommendations

B	HR and BR should be monitored, particularly during the acute phase of the illness.
√	Using a severity scale may be useful in monitoring clinical progression and response to treatment in patients with acute bronchiolitis.

7.4. Monitoring Apnoea

Questions to Answer

- In patients with acute bronchiolitis, when is apnoea monitoring indicated?

Neither CPGs nor SRs address the issue of whether apnoea should be monitored in patients with acute bronchiolitis. However, some of them do state that bronchiolitis patients may present apnoea, particularly very small infants and those with a history of prematurity or low birthweight, and that apnoea is grounds for referral to hospital. Only the CCHMC's CPG[2] states that HR and BR must be monitored (it does not mention apnoea specifically) during the acute phase of the illness, due to the risk of apnoea or bradycardia, particularly in high-risk patients (premature infants and those with underlying disorders).	CPGs
The AAP's CPG[1] mentions that apnoea is associated with a greater risk of PICU admission. A retrospective study[6] observes that one of the main factors determining severe progression in PICUs is apnoea on admission.	CPG Descriptive, 3
The information provided in Willwerth's retrospective study[33] is consistent with that of CPGs. 2.7% of patients in the study presented apnoea, and it was associated with younger age, younger post-conception age, prematurity and previous episodes of apnoea. Risk factors: age < 1 month in those born at term, post-conception age < 48 weeks in premature infants and apnoea have a sensitivity of 100%, a specificity of 64% and a negative predictive value of 100%.	CH, 2-

Recommendations

D	Apnoea should be monitored in bronchiolitis patients aged under 1 month, those with a history of prematurity and those in whom a previous episode of apnoea is reported.

8. Prevention

8.1. Palivizumab

Questions to Answer

- In children aged under 24 months, are anti-RSV (syncytial respiratory virus) monoclonal antibodies useful in preventing the onset of bronchiolitis or in reducing clinical severity if it develops? Are they particularly indicated for a specific population or a high-risk population?
- In what patients is it viable, in terms of cost/benefit, to administer anti-RSV monoclonal antibodies in order to prevent acute bronchitis? Is it viable to administer them as treatment during the acute phase?

CPGs

The evidence[1,2,4] consulted, excluding the CPG of the NZGG[12] which does not address this issue, is consistent, and concludes that administering palivizumab reduces hospital admission rate but not length of hospital stay, need for oxygen or mechanical ventilation or mortality in the patients studied (children aged under 2 years) with a history of prematurity, 35 weeks' gestation, bronchopulmonary dysplasia or congenital heart disease. The recommendations for use, based on well-designed clinical trials, are similar in all the CPGs: palivizumab should be administered only to patients selected as being premature, with bronchopulmonary dysplasia or congenital heart disease. Some also include patients with immunodeficiencies, although there are no studies in these patients [AAP[1], CCHMC[2] and SIGN[4]]. Furthermore, based on observational studies and expert opinions, one of the CPGs recommends a monthly administration of 15 mg/kg for 5 months (from November to March, i.e. during the RSV season) [AAP[1]]. The main studies on which these documents are based are a well-designed RCT, carried out in 139 hospitals with 1,502 patients, which examines premature infants with bronchopulmonary dysplasia up to 2 years old, but premature infants without dysplasia are only included up to the age of 6 months at the start of the RSV season (The IMpact-RSV study group. *Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics.1998;102 :531 537)* and another well-designed RCT performed on 1,287 patients, including patients with congenital heart disease, up to the age of 2 at the start of the RSV season (Feltes TF, Cabalka AK, Meissner HC, et al. *Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr. 2003;143:532-40)*

The AAP's[1] CPG says that both palivizumab and anti-RSV immunoglobulins, have been shown to reduce the hospital admission rate in high-risk patients, but do not reduce mortality. The advantage of palivizumab is that anti-RSV immunoglobulin interferes with the yearly vaccination schedule and requires hospital admission, its administration carries a risk of transmitting diseases and it cannot be administered to patients with heart disease because it may increase their mortality rates. However, the advantages of immunoglobulin are that it prevents not only RSV infection but all respiratory infections and otitis. The CPG also mentions the importance of informing families of preventive measures: washing hands and avoiding crowds, tobacco and nursery schools

Both the AAP's CPG[1] and one SR[103] address the efficacy of these treatments not in preventing infection but in treating it. They conclude that neither immunoglobulins nor palivizumab have demonstrated efficacy in treating RSV infection.

CPGs
SR RCT, 1++

Frogel[104] provides a study in which patients for whom palivizumab is indicated and who receive it at home show better compliance and fewer admissions due to RSV.

Descriptive, 3

Figueras Aloy[18] published the recommendations of the Spanish Society for Neonatology (SEN) on the use of palivizumab; the indications are similar to those proposed in other documents. Another article by the same author[105] describes the methods used to achieve multidisciplinary consensus on measures to prevent syncytial respiratory virus infection. The results regarding indications for palivizumab corroborate the SEN's proposals and add another two indications (transplant recipients and patients with immunodeficiencies).

Review and consensus document, 4

Another study[88] examines patients with underlying disorders receiving intravenous palivizumab for RSV infections, rather than bronchiolitis patients. 80% of those who have been given intravenous palivizumab also receive ribavirin. The progression of all patients is described, and the survival rate is high, but it is difficult to establish what role is played in this by palivizumab and ribavirin.

Descriptive, 3

The NZGG's CPG[12] is the only one not to address the cost-effectiveness of palivizumab as prophylactic treatment. CPGs[1,2,4] and SRs[106-108] are highly consistent, and conclude that palivizumab treatment is not cost-effective if used in the groups for which it is recommended, and may only be cost-effective in even more select subpopulations. The AAP's CPG[1] mentions that these results may change if prophylaxis is shown to be effective not only in reducing hospital admissions but also in reducing outpatient consultations, and if the use of palivizumab reduces wheezing and long-term airway problems.

CPGs

Three [SRs106-108] have been found on the financial viability of immunoprophylaxis for RSV. Kamal-Bahl[106] evaluates both palivizumab and anti-RSV immunoglobulin, and finds that both treatments prove cost-effective only in some subpopulations among high-risk patients. The other two [SRs107,108] evaluate only palivizumab, and also conclude that it this is only cost-effective when administered in high-risk patient subgroups, specifically[108] those with chronic lung disease and two or more additional risk factors.

SRs, 1++, 1+

Recommendations

A	Palivizumab reduces the number of hospital admissions due to RSV in high-risk patients. It has not been shown to reduce the incidence of the illness; the duration of hospitalisation, oxygen therapy or mechanical ventilation; or mortality.
A	Palivizumab prophylaxis is considered advisable for the prevention of severe lower respiratory tract diseases that require hospitalization, caused by RSV during the periods when there is an expected risk of infection due to RSV, in: • Children under 2 years who have required treatment for bronchopulmonary dysplasia in the last 6 months. • Children under 2 years with haemodynamically significant congenital heart disease. • Infants born at 35 weeks' gestation or less, who are 6 months old at the start of the RSV season or who are discharged from hospital during the RSV season.
C	In cases for which palivizumab prophylaxis is indicated, it should be administered from October to March as a monthly intramuscular dose of 15 mg/kg.
D	In patients for whom it is indicated, home administration of palivizumab may improve compliance and reduce the number of hospital admissions due to RSV.
A	Palivizumab has not been shown to be effective in treating established RSV infections.
√	Palivizumab reduces the rate of hospital admission due to RSV but does not prevent infection in all cases. It does not prevent other viral infections related to acute bronchiolitis. Hygiene measures must therefore be emphasised.

The CPG recommendations on palivizumab prophylaxis for preventing severe lower respiratory tract diseases caused by RSV which require hospitalization, are based on the therapeutic indications of the drug described in its summary of product characteristics. In Spain, in 2005[105] the Spanish Society for Neonatology (SEN) published its recommendations on the use of palivizumab and with the aim of increasing efficiency in the use of this drug, significantly reduced (by 13-17% of the potential size indicated in the drug's summary of product characteristics) the number of patients that are candidates to receive prophylaxis in the segment between 32.1 and 35.0 weeks' gestational age. In this segment the use of palivizumab is advised only in patients who also have two or more risk factors, identified as such by multi-centre studies conducted in Spain. These risk factors are:

- Chronological age under 10 weeks at the beginning of the season.
- No breast feeding or less than 2 month's breast feeding (due to medical indication).
- At least one school-aged sibling (<14 years old).
- Nursery school attendance.
- Family history of wheezing.
- Overcrowding at home (4 adults).
- Airway malformations, neuromuscular disease.

The SEN widens the patients that are candidates for receiving prophylaxis, in the group of less than 29 weeks' gestational age, to infants who are 12 months old at the start of the RSV season, due to the special vulnerability of these patients.

8.2. Measures to Prevent Community Transmission

Questions to Answer

- What measures are useful in preventing community transmission of RSV and other respiratory viruses?

Only the CCHMC's CPG[2] deals with this subject, and it does not justify its recommendations by referring to its bibliography. Other CPGs either do not address the issue or say that there is no evidence on the subject. The SIGN's CPG[4] devotes a section to explaining the infection characteristics of RSV and says that it is highly contagious; it is transmitted in secretions and on fomites (clothes, hands, etc.), where it may remain viable for up to 12 hours; particles bearing the virus have been found up to 2 metres from the patient following a sneeze or cough; it penetrates the host via the mucous membranes (eyes, nose and mouth); it is destroyed by soap and water or alcohol gels; and immunocompromised children may take more than 3 weeks to eliminate it. CPGs

The CCHMC's CPG[2] recommends advising parents before children are discharged from hospital, at birth and at follow-up visits up to the age of 1 year to limit exposure to environments where infection may be present and exposure to children, and emphasising the importance of hand-washing in all environments (expert opinion).

One review article[109] makes similar recommendations. It states that RSV infections generally last for 3-4 days but may last for up to 4 weeks, and that RSV can survive for 30 minutes or more on the hands and clothes, and for hours on toys, counters and other surfaces. It also highlights that hand-washing is the best way to prevent dissemination and infection, and recommends that home care nurses who care for premature infants should emphasise the importance of hand-washing by the whole family and ensure that they do so. Other measures recommended are limiting the number of visitors, avoiding nursery school attendance, recommending that carers do not smoke or at least do not do so around the child and remembering that tobacco particles that cling to clothes can also harm the child. It recommends that carers be educated on the signs and symptoms of RSV infection and mentions that where palivizumab is indicated it can be administered by home care nurses. Review, 4

Recommendations

D	Carers should be informed of the benefits of washing their hands in order to prevent transmission of respiratory viruses. They should be advised to wash their hands frequently.

D	Numbers of visits should be limited, particularly visits to very small and premature infants.
D	Contact with people with symptoms of respiratory infections and environments with a high risk of contagion should be avoided.
D	Tobacco exposure should be avoided. Carers should be informed that tobacco particles that cling to clothing may harm children even if no one smokes around the child.
√	Parents must be informed of these preventive measures before children are discharged from hospital, at birth and at follow-up visits up to the age of 1 year.
D	Carers should be educated on the signs and symptoms of acute bronchiolitis.

8.3. Measures to Prevent Hospital Transmission

Questions to Answer

- What measures are useful in preventing hospital transmission of RSV and other respiratory viruses?

Characteristics of the virus: The CPGs of SIGN[4] and the AAP[1] mention the characteristics of RSV: it is highly contagious; it penetrates the body via the mucous membranes of the eyes, nose or mouth; it is transmitted via secretions on the hands or fomites, where it may survive for 6-12 hours; drops of secretions may be scattered up to 2 metres by a cough or sneeze and may be found up to 6 metres from the patient on objects such as toys; it is destroyed by soap and water or alcohol gel; and in immunocompromised children it can be isolated for more than 3 weeks. CPGs

Disinfecting hands: All CPGs agree that decontaminating the hands before and after handling the patient is the most important measure in reducing hospital RSV transmission (grade B, AAP[1] and CCHMC[2]; grade D, SIGN[4]; expert opinion, NZGG[12]). The AAP's CPG[1] mentions that alcohol gels are more effective in decontaminating the hands than hand-washing, although the latter is equally valid. CPGs

Use of gloves, doctor's coats and masks: The CPGs of SIGN[4] and the CCHMC[2] (grade D) and the AAP's CPG[1] recommend the use of gloves with or without a doctor's coat (the CCHMC's CPG[2] also recommends facemasks with grade D) as well as hand-washing. In contrast, the NZGG's CPG[12] states that there is insufficient evidence on the use of gloves and doctor's coats. The Pediatric Special Interest Group (PSIG) of the Society for Healthcare of America[110] recommends putting on a doctor's coat and gloves before entering patients' rooms and using a mask until flu or an adenovirus infection has been ruled out.

CPGs

Review, 4

Isolation and establishing cohorts: If patients cannot be placed in single rooms, hospital cohorts should be established according to whether or not patients present RSV infections. SIGN's CPG[4] recommends performing an RSV test on all patients under the age of 2 years with respiratory infections who require hospital admission (grade D). The Pediatric Special Interest Group (PSIG) of the Society for Healthcare Epidemiology of America[110] recommends placing patients in single rooms where possible, and establishing hospital cohorts if this is impossible.

CPGs

Review, 4

Other measures: The CPGs of the AAP[1] and SIGN[4] assert that educating staff and family members and monitoring the beginning of the RSV season have been shown to be effective in controlling the spread of RSV. They recommend monitoring the use of measures to prevent hospital transmission of RSV (grade D, SIGN[4]). SIGN's CPG[4] mentions that people with upper respiratory tract infections are a risk, and that they should not be allowed to enter hospitals. The Paediatric Special Interest Group (PSIG) of the Society for Healthcare Epidemiology of America[110] recommends restricting visits by people with symptoms of respiratory infection.

CPGs

In line with the above, Simon[111] observed a decrease in the incidence of hospital infection from 1.67 to 0.18 per 1,000 patients admitted, and a decrease in the incidence of hospital infection from 1.1 to 0.1% after control measures were applied (**informing healthcare staff** of transmission routes, **isolating patients or establishing hospital cohorts**, **identifying RSV patients** using an RSV test, using contact measures: **disinfecting hands and medical materials**, **wearing doctor's coats, masks and gloves**, **daily disinfection of contact surfaces** in patients' rooms). These measures were inspected twice a week.

Review, 4

Descriptive, 3

Two studies[112,113] describe the measures used to prevent an outbreak when a case of RSV is identified in a more select subgroup of patients: inpatients at neonatal intensive care units. A satisfactory result is found by closing the unit to new admissions and limiting entry to the unit, establishing cohorts, using contact measures (doctor's coats, gloves and masks) and administering palivizumab. It remains unclear whether the use of palivizumab is necessary in all cases or only in certain circumstances, such as when other control measures fail.

Descriptive, 3

Review, 4

Recommendations

D	RSV is highly contagious and penetrates the body through the mucous membranes of the eyes, nose or mouth. It is transmitted in secretions on the hands or on fomites, where it can survive for 6-12 hours. Droplets of secretions may be scattered up to 2 metres. RSV is destroyed by soap and water or alcohol gel.
D	Medical staff and those accompanying patients must be informed of the routes of transmission and control measures.
B	Hand-washing is the most important measure in preventing hospital transmission of RSV. Hands must be decontaminated before and after direct contact with patients, after contact with inanimate objects from the patient's surroundings and after removing gloves. Alcohol gels are recommended to disinfect the hands.
D	Contact measures (particularly doctor's coats and disposable gloves) are recommended.
D	Surfaces that come into contact with patients with acute bronchiolitis and medical materials from their surroundings should be disinfected.
D	Patients with acute bronchiolitis should be isolated. If this is not possible, hospital cohorts should be established by aetiology.
D	Visits by people with symptoms of respiratory infections should be restricted.
D	Compliance with control measures must be monitored.
D	Hand disinfection and isolation of contact, closure of units (closure to new admissions and restrictions to entry), establishing cohorts and palivizumab appear to be useful in controlling outbreaks of RSV infection in Neonatal Intensive Care Units.

8.4. Smoking

Questions to Answer

- In patients with acute bronchiolitis, what is the relationship between maternal smoking during pregnancy and passive exposure of children to tobacco smoke and the incidence and severity of the illness?

All CPGs[1,2,4,12] agree that exposing children to tobacco smoke should be avoided (grade A, NZGG[12]; grade B, AAP[1]; grade C, SIGN[4]; expert opinion, CCHMC[2]), because passive tobacco exposure increases the incidence of respiratory infections and the risk of being admitted to hospital with this type of infection. A study of bronchiolitis patients[20] is consistent with this statement: it finds that environmental exposure to tobacco smoke exacerbates symptoms and worsens the prognosis of patients with acute bronchiolitis.

CPGs

Descriptive, 3

SIGN's CPG[4] mentions that there is evidence of a weak association between hospital admission due to RSV and smoking during pregnancy, but this relationship is not mentioned in any other CPGs. More recent work[15,16,18] confirms this association: the first two studies find a greater risk of acute bronchiolitis, and a greater risk of hospital admission due to RSV infection in children whose mothers smoked during pregnancy. CH, 2+

Recommendations

C	Maternal smoking during pregnancy seems to increase the risk of acute bronchiolitis. Smoking should be avoided during pregnancy.
A	Exposure to tobacco smoke increases the rate of hospital admission due to lower respiratory tract infections, including bronchiolitis.
D	Exposure to tobacco smoke exacerbates symptoms and worsens the prognosis of patients with acute bronchiolitis.

8.5. Breastfeeding

Questions to Answer

- In patients with acute bronchiolitis, what is the relationship between breastfeeding and the incidence and severity of the illness?

With the exception of the CCHMC's CPG[2], which does not cover the subject, all CPGs recommend breastfeeding (grade A, NZGG[12]; grade B, AAP[1]; grade C, SIGN[4]), because it provides protection against respiratory infections and reduces the risk of hospital admission due to RSV. The NZGG's CPG[12] also states that protection is greater if breastfeeding is continued for more than 4 months (grade A). The AAP's CPG[1] explains this protection: breast milk has been shown to contain anti-RSV immune factors, including immunoglobulins G and A and interferon. It has also been shown to have a neutralising effect on RSV. CPGs, Review, 4

Chatzimichael[20] presents a descriptive study which finds that breastfeeding has a protective effect. The effect is sufficiently powerful to protect even patients exposed to tobacco. Descriptive, 3

A cohort study[15] found that patients who were not breastfed were at more risk of acute bronchiolitis. CH, 2+

Dornelles[19] finds that the length of breastfeeding (whether alone or combined with bottle-feeding) was associated with better progression (shorter oxygen therapy or hospital stays). In contrast, Figueras-Aloy's study[18] found no relationship between the length of breastfeeding and hospital stays due to RSV.	CH, 2- CC, 2+

Recommendations

A	Breastfeeding protects infants against lower respiratory tract infections, including bronchiolitis.
A	Breastfeeding for more than 4 months offers greater protection against lower respiratory tract infections.
D	Breastfed infants seem to be at less risk of acute bronchiolitis and less risk of severity if it does develop.

9. Progression

9.1. Duration of Clinical Presentation, Hospital Admission Rate

Questions to Answer

- What is the usual duration of signs and symptoms in patients with acute bronchiolitis? What percentage of patients with acute bronchiolitis are admitted to hospital? Of these, how many are admitted to PICUs?

CPGs

SIGN's CPG[4] concludes that the **average length of acute bronchiolitis is approximately 12 days**. This is based on three high-quality studies: an RCT on inhaled steroids, which found that the time at which half the patients in the placebo group were asymptomatic for more than 48 hours was 12 days; a cohort study that involved telephone interviews and found that the average duration of symptoms was 12 days (although **symptoms were still present after 28 days in 9% of cases**); and another study that found an average duration of coughing of 12 days, an average duration of **wheezing and feeding difficulties of 7 days** and an average duration of **breathing difficulties of 6 days**. The CPGs of the NZGG[12] and the CCHMC[2] both base their information on the same cohort study (Swingler, 2000), and therefore also conclude that symptom duration is approximately 12 days. The AAP's CPG[1] does not address this issue.

SIGN's CPG[4] also includes information from a study on **ciliary damage**, which according to the study lasts **between 13 and 17 weeks**. SIGN's CPG[4] mentions that there were fewer doctor's consultations when carers knew how long the illness lasts. Like the NZGG's CPG[12], it therefore recommends informing parents of the duration of the illness (grade B, SIGN[4] and NZGG[12]).

According to SIGN's CPG[4], **70% of all children contract an RSV infection before the age of 1 year**, and **22% develop symptoms**, but only **3%** of all children aged under 1 year will need to be **admitted to hospital due to bronchiolitis**. Like the CCHMC's CPG[2], it also states that the hospital admission rate has increased over the last 10 years. The AAP's CPG[1] states that RSV infection leads to more than 90,000 hospital admissions per year (this figure is understood to refer to the USA), but does not state any rates.

None of the CPGs provides PICU admission rates.

65% of children are said to suffer respiratory infection[114 (descriptive)] **before the age of 1 year**, and 13% are said to **present bronchiolitis**[115 (CH)]. Carrol[116 (CH)] finds that before the age of 1 year 13.3% of children attend outpatient appointment for bronchiolitis, 6.2% attend the Accident & Emergency ward and **5.5%** are **admitted to hospital**. Koehoorn[115 (CH)] finds a lower **admission rate**: **1.7%**. Mansbach[30 (CH)] says that **40% of patients who attend Accident & Emergency are hospitalised**, and gives a **PICU admission rate of 3%**. In inpatients, an average duration of **oxygen therapy of 56 hours** is given[100 (descriptive)]. The Cochrane review[63] on hypertonic solution describes a **duration of hospital stays of between 3.5 and 4 days** in the placebo group, and between 2.6 and 3 days in the treatment group. Regamey[114 (descriptive)] states that **20% of patients present positive virus tests 3 weeks** after the onset of respiratory infection.	SR RCT, 1++ CH 2+ Descriptive, 3

Recommendations

B	Up to 70% of all children contract an RSV infection before the age of 1 year. 22% develop symptoms.
C	Approximately 13% of children develop acute bronchiolitis before the age of 1 year.
C	2-5% of infants require hospitalisation for acute bronchiolitis before the age of 1 year.
C	3% of children seen in Accident & Emergency wards and up to 20% of inpatients may be admitted to PICUs.
B	The usual duration of symptoms is 12 days (although 9% may still present symptoms at 28 days), but only 6-7 days of respiratory difficulty and feeding difficulties.
B	It should be explained to parents/carers that acute bronchiolitis may take several weeks to resolve.
D	Among those admitted to hospital, the average duration of hospitalisation is given as approximately 3 days, with an average of 56 hours' oxygen therapy.
D	Up to 20% of viral tests have been found positive 3 weeks after symptom onset.

9.2. Recurrent Wheezing

Questions to Answer

- Do patients with acute bronchiolitis have a higher risk of developing recurrent wheezing/asthma?
- In patients with acute bronchiolitis, do anti-RSV monoclonal antibodies reduce the risk of developing recurrent wheezing/asthma?

The relationship between acute bronchiolitis and subsequent **recurrent wheezing** has been described, although the CPGs do not provide any recommendations on the subject.

One systematic review[116] and only two of the CPGs[4,12] address this subject. They conclude that acute bronchiolitis and infection are associated with recurrent wheezing. There is a marked fall in the incidence of these episodes as patients' age increases. They are particularly common before the age of 1 year, and are relatively frequent up to 5-6 years of age (at 5 years, recurrent wheezing is found in 40% of children). The association disappears from the age of 13 years.

SR, RSV 1+

Hyvärinen[117] studies the incidence of asthma (continuous or intermittent use of inhaled anti-inflammatories or recurrent wheezing with a positive exercise test) and lung function 11 years after suffering acute bronchiolitis. 40% of children are found to present asthma. However, bronchiolitis due to RSV is associated with a restrictive (low FVC, normal FEV_1) rather than an obstructive pattern, and no association is found between aetiology of rhinovirus or RSV and bronchial hyperresponse measured via an exercise test or methacholine test.

Descriptive, 3

According to García-García's work[50], patients with bronchiolitis due to RSV are not alone in presenting a subsequent recurrent wheezing. In fact, in this study the main risk factor for asthma was bronchiolitis caused by metapneumovirus, followed by bronchiolitis due to RSV.

CH, 2-

A large-scale population study[118] found that children aged 4 months during the seasonal peak for respiratory viruses were at most risk of developing acute bronchiolitis and of childhood asthma. Although no direct relationship can be established, this finding suggests that there may be a relationship between acute bronchiolitis and asthma.

Descriptive, 3

The studies that investigate whether **administering anti-RSV monoclonal antibodies reduces the risk of recurrent wheezing/asthma** involve hospitalised children. This means that the information they contain cannot be extrapolated to all children with acute bronchiolitis. It is not known whether this association is secondary to the damage done by the infection that causes acute bronchiolitis, or if there is a prior genetic or environmental predisposition. One study[119] found that high-risk patients who had received prophylactic treatment with anti-RSV immunoglobulin showed better lung function, less atopy, less school absence and less asthma than those who had **not**.

CH, 2-

Only one study[120] has been found on the efficacy of palivizumab treatment in reducing recurrent wheezing. This was conducted in premature infants and compared those who received palivizumab with those who should have received it but did not. The groups had different baseline characteristics (age, birthweight, number of siblings, number of siblings attended nursery school, percentage of premature births). The patients treated with palivizumab presented a lower incidence of recurrent wheezing and more time before their first episode of wheezing.

CH, 2-

Recommendations

A	Patients with acute bronchiolitis may present recurrent wheezing.
A	Recurrent wheezing is more common up to the age of 5 years. Incidence falls as patients' age increases.
D	It is not known whether recurrent wheezing is secondary to damage done by the infection that causes acute bronchiolitis or if there is a prior genetic or environmental predisposition.
D	Palivizumab prophylaxis in premature infants may reduce the incidence of recurrent wheezing, but more studies demonstrating this are required.

10. Dissemination and Implementation

There are various different versions of CPGs: full, summary, information for patients and a quick-consultation tool. All these versions are available in HTML and PDF format from the GuíaSalud website (www.guiasalud.es). A hard copy of the summary version containing a CD-ROM of the full version is also published. CPGs are useful in improving healthcare and patient outcomes. Currently, the main challenge is to achieve compliance by professionals. The implementation plan for the guideline on acute bronchiolitis includes the action outlined below.

Dissemination and Implementation Strategies:

- Official presentation of the guideline by healthcare authorities.
- Copies sent individually to professionals and potential users.
- Distribution of material for patients.
- Dissemination of the guideline in electronic format on the websites of healthcare services and scientific societies involved in the project.
- Presentation of the guideline at scientific events (conferences, meetings).
- Publication of the guideline in medical journals.

Proposed Evaluation Indicators

With the help of colleagues and external reviewers, the authors of the CPG have designed a set of indicators, in order to provide tools to evaluate the degree of compliance with the CPG's main recommendations. These indicators are based on the recommendations backed up by the greatest amount of evidence and/or the most consensus among the guideline's authors.

- Suitable referral rate (referral from primate care with admission/referral from primary care).
- Rate of repeat attendance of Accident & Emergency wards with admission.
- Readmission rate.
- Average length of hospital stay of inpatients.
- Rate of palivizumab treatment adjustment.

- Steroid administration rate.
- Ipratropium bromide administration rate.
- Administration rate of mucolytics, antitussives or similar.
- Antibiotic administration rate.
- Number of chest X-rays performed.
- Number of blood tests performed.
- Number of virus tests performed in outpatients.
- Monitoring of the use of isolation measures in inpatients.
- Number of patients receiving non-invasive ventilation.
- Number of patients receiving conventional mechanical ventilation.

11. Recommendations for Future Research

- Studies to validate a severity scale for acute bronchiolitis.
- Studies into the prevalence of acute bronchiolitis.
- Studies on the benefits of transcutaneous capnometry in patients with acute bronchiolitis.
- Studies on safe haemoglobin saturation levels when deciding whether to administer additional oxygen.
- Studies on clinical presentation, progression and response to treatment according to viral aetiologies.
- Studies on respiratory physiotherapy techniques other than vibration/percussion.
- Studies on the development of vaccines for the viruses that cause bronchiolitis.
- Studies on the relationship between the genome and severity of acute virus-induced bronchiolitis.
- Studies on the relationship between innate immunity and severity of acute bronchiolitis.
- Studies that assess the possible synergy of nebulised adrenaline and oral dexamethasone as treatment.
- Studies on the benefits of all forms of non-invasive ventilation.
- Studies on the benefits and side effects of nebulised hypertonic saline solution.

Appendices

Appendix 1: Key to Evidence Statements and Grades of Recommendations from SING

Levels of evidence	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
3	Non-analytic studies, e.g. case reports, case series.
4	Expert opinion.
Grades of recommendations	
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+.
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++.
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+.

Studies classified as 1- and 2- should not be used in the process of developing recommendations due to their high possibility of bias.

Good practice points

√	Recommended best practice based on the clinical experience of the guideline development group.

Source: Scottish Intercollegiate Guidelines Network. SIGN 50: A guideline developers' hand-book (Section 6: Forming guideline recommendations), SIGN publication n.º 50, 2001.

[1] Sometimes the guideline development group becomes aware that there are some significant practical aspects they wish to emphasise and for which there is probably no supporting scientific evidence available.
Generally, these cases are related to some aspect of the treatment, considered to be a good clinical practice and that nobody would normally question.
These aspects are considered good clinical practice points.
These messages are not an alternative to evidence based recommendations, but must be only considered when there is not another way to highlight the aspect mentioned above.

Appendix 2: Information for Patients

What is bronchiolitis?

Bronchiolitis is a respiratory infection caused by a virus, in which the bronchi and bronchioles, the smallest airways or tubes which carry air inside the lung, become inflamed.

It affects children less than 2 years old, especially those less than 6 months old.

The virus that causes bronchiolitis most often is RSV: respiratory syncytial virus. In Spain, this virus is most common between November and March.

Most children catch RSV when they are small, but only some develop bronchiolitis. Most children who develop bronchiolitis suffer only mild symptoms, and only a few need to be admitted to hospital.

How is it caught?

The main way to catch bronchiolitis is by touching objects that have been contaminated with the virus (for example, toys, dummies or other objects on which drops of saliva or mucus containing the virus often remain) and then touching the eyes, nose or mouth. It can also be caught by inhaling infected particles from another person, in other words breathing in small droplets that are produced when someone who has the virus coughs or sneezes.

What are the symptoms?

At the beginning of the illness, children usually display cold-like symptoms (increased mucus production and a cough).

Later on, the bronchioles become inflamed, making it harder for air to flow through them. This may cause breathing difficulties (rapid breathing, with the ribs clearly visible or a lot of tummy movement) and wheezing or other sounds when the child's chest is listened to.

As a result, some children may find it difficult to feed, and may vomit and/or choke.

Patients with bronchiolitis may have a high temperature, although they do not usually have bacterial infections at the same time that need to be treated with antibiotics.

When should I consult my paediatrician?

If you suspect that your child is breathing faster or with more difficulty than usual, consult your paediatrician so that he/she can examine your child.

Seek urgent medical help if:

- Your child's breathing is very agitated.
- His/Her skin is sinking between the ribs.
- He/She is finding it difficult to feed.
- He/She is very agitated or very soundly asleep.
- He/She has a very high temperature.
- He/she grunts when he/she breathes.
- His/her lips or nails are bluish, either spontaneously or when he/she coughs.
- There are pauses in his/her breathing.

Are some children more susceptible to bronchiolitis than others?

Yes: those born prematurely and those with other health problems, such as heart disorders, lung disorders or immune-system deficiencies. Particular care must be taken to prevent the illness in these children.

During the respiratory virus season (autumn and winter), for some of these children it may be useful to give monthly treatment with an antibody (defences) against RSV, called palivizumab, to prevent bronchiolitis. This treatment is usually given at the hospital where these patients undergo their regular check-ups.

What examinations may be needed during the infection?

When it is clear that a child has bronchiolitis, no examinations are usually needed.

If your child needs to be admitted to hospital, your doctor may take a sample of nasal mucus to find out what virus is causing the infection. This is so that he/she can be kept apart from children with other viruses.

While in hospital, blood oxygen levels are usually measured either continuously or occasionally, using a sensor that emits a red light. This is usually placed on the fingers or toes.

If a child has a high temperature or his/her progression is unusual, a chest X-ray and urine or blood tests may sometimes be useful.

How long does it last?

In previously healthy children, the illness lasts between 7 and 12 days, although the cough may continue for many more days.

Some children may experience breathing difficulties again when they catch another cold after they have had bronchiolitis, particularly during the first year after bronchiolitis.

You should always consult your paediatrician if your child experiences breathing difficulties or any of the warning symptoms mentioned above.

What treatment can I provide at home?

Babies breathe mainly through their noses. If their noses are blocked by mucus, they may find it difficult to breathe. Because of this, you should clear his/her nasal cavities by giving him/her a nasal lavage (inserting saline solution and aspirating mucus) before your baby feeds or sleeps.

Raising the head of the bed/cot slightly helps children breathe a little more easily.

If your child has a high temperature, you can give him/her anti-fever medicines such as paracetamol or ibuprofen (ibuprofen can only be given to children more than 6 months old) and use physical methods (removing clothes and blankets or giving lukewarm baths).

Children with bronchiolitis have little appetite. They get tired easily while feeding and may vomit or choke. To help them, feeds should be broken up (give less food but more often).

Most medicines which have been tested for bronchiolitis have not been shown to improve symptoms. However, your paediatrician may prescribe an inhaled treatment. Do not use any medicine not prescribed by your doctor.

What treatments must NOT be used for bronchiolitis?

Cough syrups, mucolytics (expectorants) and nasal decongestants must not be used. They may be harmful.

Should children with bronchiolitis be given antibiotics?

Bronchiolitis is caused by viruses. This means **it does not respond to antibiotic treatment**.

How can I prevent bronchiolitis?

Bronchiolitis is transmitted from person to person. This means that people with respiratory infections, even just a cold, should wash their hands frequently, especially before and after touching the child or any object the child uses.

It is also important to avoid crowded places, particularly places where there are a lot of children (e.g. nursery schools and playgroups).

Exposure to tobacco smoke must be completely avoided.

Breastfeeding is recommended, as breastfed children are better protected against bronchiolitis.

There is no vaccine to prevent this illness yet, although a vaccine is being researched and developed.

Appendix 3: Glossary

Randomisation: A procedure by which sample selection or allocation to a treatment option or placebo is carried out at random.

Cochrane Library: A database on effectiveness produced by the Cochrane Collaboration. It consists of the organisation's original systematic reviews and other items.

Comorbidity: The presence of several additional or associated illnesses.

Effectiveness: The result of a diagnostic, preventive or therapeutic action when applied in normal practice, under non-experimental conditions.

Efficacy: The result of a diagnostic, preventive or therapeutic action when applied under experimental and/or controlled conditions, e.g. in a clinical trial.

Clinical trial: An experimental study to evaluate the efficacy and safety of a treatment or action.

Randomised clinical trial: A type of clinical trial in which patients are allocated at random to the various treatments being compared.

Statistically significant: In a study, if the probability that the differences in effect found when two groups are compared is lower than a previously-defined significance level, the differences are said to be statistically significant. This means that the differences observed between the treatments or groups compared are highly unlikely to have occurred by chance. A significance level of 5%, generally written as $p<0.05$, is usually used. However, it should be borne in mind that even if the difference between treatments is statistically significant, this does not always indicate that the difference is «clinically significant» or relevant.

Before-and-after study: A study in which the same group of people is evaluated both before and after an action or treatment.

Blind study: A study in which one of the parties involved does not know who is receiving a particular treatment option or placebo. Blinding is used to prevent research results being influenced by the placebo effect or by observer bias. In order to evaluate binding effectively, we need to know who has been blinded for the study (patients, investigators, healthcare professionals, results allocators and/or statisticians).

Case and control study: This is an observational epidemiology study in which study subjects are selected according to whether they have (cases) or do not have (controls) a particular illness, or a particular effect in general. Once the individuals in each group have been selected, it is investigated whether or not they were exposed to a certain feature, and the proportion of people exposed in the case group is compared with the proportion in the control group.

Cohort study: This consists of monitoring one or more cohorts of individuals with varying levels of exposure to a risk factor, in whom the onset of the illness or condition being studied is measured.

Evidence: Proof. Evidence-based medicine: medicine based on scientific proof.

Confusing factor: This is a variable that distorts measurement of the association between another two variables being studied. A confusing factor may lead to a non-existent effect apparently being observed or a real association being exaggerated (positive confusion); or, in contrast, it may lead to a real association being weakened or even the direction of a real association being reversed (negative confusion).

Risk factor: Any circumstance that increases the probability of someone contracting a particular disease.

Clinical practice guideline: A set of instructions, directives, statements or recommendations developed systematically in order to help professionals and patients take decisions on the appropriate healthcare for specific clinical circumstances.

Incidence: The number of new cases of a disease arising in a population over a particular period of time. This indicates the probability of an individual without the disease developing it within a particular period.

Confidence interval: The interval at which the actual effect size (never known exactly) is found with a pre-established level of security, or confidence. We often speak of a «95% confidence interval» (or «95% confidence limits»). This means that the actual value would be within this interval in 95% of cases.

Meta-analysis: A statistical technique that allows the results of several different studies (studies of diagnostic tests, clinical trials, cohort studies, etc.) to be combined in a single estimate which lends more weight to the results of larger studies.

Morbidity: Disease caused.

NICE: An institution within the UK's NHS. Its role is to provide doctors, patients and the general public with the best available evidence, mainly in the form of clinical guidelines.

NNT/NNH: This is a measure of the efficacy of a particular treatment. The number needed to treat (NNT) is the number of people that need to be given a specific treatment to cause or prevent an additional event. Similarly, the number needed to harm (NNH) is defined to evaluate adverse effects.

Odds ratio (OR): A measure of the efficacy of a particular treatment. An odds ratio of 1 means that the effect of the treatment is no different from the effect of the control. An OR greater (or less) than 1 means that the effect of the treatment is greater (or less) than that of the control. Note that the effect measured may be either negative (e.g. death or incapacity) or positive (e.g. giving up smoking).

Percentile: A value that divides an ordered set of statistical data so that a certain percentage of the data fall below this value. One of the ninety-nine points that divides a distribution into a hundred parts with the same frequency.

Placebo: An inactive substance or action used as a control in clinical research. It serves to rule out cures for unknown reasons which would not be attributable to be treatment being researched.

Statistical power: The ability of a test to detect differences of a particular size between groups being compared as statistically significant.

Prevalence: The proportion of individuals in a population who have a particular disease or characteristic at a particular point in time or during a particular period of time. This indicates the probability of an individual from a certain population having a disease at a particular point in time or during a particular period of time.

Cochrane review: A systematic review carried out according to the methods of the Cochrane Collaboration and published in the Cochrane Library.

Systematic review (SR): A review in which the evidence on a particular subject has been systematically identified, evaluated and summarised according to a pre-established set of criteria. It may or may not include meta-analysis.

Relative risk (RR): The quotient between the rate of events in a treatment group and a control group. This value is interpreted in the same way as the OR.

Clinical series: Also called a case series, this is a type of study that describes experience with a group of patients with similar diagnoses, with no comparator group.

Bias: Error appearing in the results of a study due to factors that depend on data collection, analysis, interpretation, publication or review. These factors may lead to conclusions that are systematically different from the truth or which are incorrect with regard to research aims.

SIGN: A multidisciplinary Scottish agency that publishes evidence-based clinical practice guidelines and methodological documents on guideline design.

Terms relating to methodological issues are based on the glossary of CASPe (Critical Appraisal Skills Programme Español), available at http://www.redcaspe.org/homecasp.asp.

Appendix 4: Abbreviations

yr(s)	year/years
AAP	American Academy of Pediatrics
CAHTA	Catalan Agency for Health Technology Assessment
AHRQ	Agency for Healthcare Research and Quality
Art	article
AB	acute bronchiolitis
CC	case-control
CCHMC	Cincinnati Children's Hospital Medical Center
CH	cohort(s)
CO_2	carbon dioxide
CPAP	continuous positive airway pressure
d	day(s)
PSBI	potentially serious bacterial illness/infection
RCT	randomised clinical trial
HR	heart rate
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in one second
BR	breathing rate
FVC	forced vital capacity
CPG	clinical practice guideline
WG	working group
hr	hour
H_2O	water
Heliox	a helium/oxygen gas mixture
hMPV	human metapneumovirus
CI	confidence interval
UTI	urinary tract infection
Kg	kilogram(s)
m	month(s)
mg	milligram(s)

ml	millilitre(s)
mmHg	millimetres of mercury
MT	meta-analysis
n	number of patients
n.º	number
NZGG	New Zealand Guidelines Group
O_2	oxygen
AOM	acute otitis media
OR	odds ratio
$PaCO_2$	partial carbon dioxide pressure in arterial blood
PaO_2	partial oxygen pressure in arterial blood
pCO_2	partial carbon dioxide pressure
CRP	C-reactive protein
PCT	procalcitonin
pO_2	partial oxygen pressure
PRISM	Pediatric Risk of Mortality score
SP	pressure support
RDAI	Respiratory Distress Assessment Instrument
rhDNase	dornase alpha
bpm	breaths per minute
RR	relative risk
SR	systematic review
RT-PCR	real-time polymerase chain reaction
chest X	chest X-ray
SIGN	Scottish Intercollegiate Guidelines Network
SpO_2	oxyhaemoglobin saturation
SIADH	syndrome of inappropriate antidiuretic hormone
PICU	paediatric intensive care unit
HFOV	high-frequency oscillatory ventilation
MV	mechanical ventilation
NIV	non-invasive ventilation
RSV	respiratory syncytial virus

Appendix 5: Disclosure of Interests

The authors', reviewers' and expert collaborators' disclosure of interests was compiled using the pre-established form included in the *Methodology Manual for Developing Clinical Practice Guidelines of the Spanish National Healthcare System*[12].

Working Group:

Rosario Cintora Cacho, Gemma Claret Teruel, Carles Luaces Cubells, Federico Martinón Torres, Jordi Pou Fernández, Jesús Sánchez Etxaniz, Marta Simó Nebot and **Maria-José Torregrosa Bertet** have declared that they are not affected by any conflicts of interest.

Eduardo González Pérez-Yarza has received financial payments (travel allowances, conferences, clinical trials) from GSK, MSD, Novartis and Abbott over the last 5 years. He is a member of Abbott Laboratories Spain's Motavizumab Advisory Committee.

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Antonio Moreno Galdó worked as a consultant for the Abbott laboratory in 2006, and for the MSD laboratory in 2008. He spoke at conferences for the Abbott laboratory in 2006 and for the MSD laboratory in 2006-2007, and worked on MSD laboratories' postgraduate courses in 2008.

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External Reviewers:

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Francisco Javier Pellegrini Belinchón held practical workshops for MSD and GSK in 2007 and 2008. In 2008 he received a research grant for his study in the field of Childhood Respiratory Disorders, *A study of wheezing in infants aged under one year in Salamanca. This was a multicentre trial.*

Appendix 6: Main Clinical Practice Guidelines

Title: Scottish Intercollegiate Guidelines Network (SIGN). Bronchiolitis in children. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2003.
Website: http://www.sign.ac.uk/guidelines/fulltext/91/index.html

Title: Diagnosis and management of bronchiolitis. American Academy of Pedia-trics Subcommittee on Diagnosis and Management of Bronchiolitis. Pediatrics. 2006 Oct; 118(4): 1774-93.
Website: http://aappolicy.aappublications.org/cgi/reprint/pediatrics;118/4/1774.pdf

Title: Wheeze and Chest Infection in Infants under 1 year. New Zealand Guidelines Group. April 2005.
Website: http://www.paediatrics.org.nz/files/guidelines/wheezeendorsed.pdf

Title: Evidence based clinical practice guideline for medical management of bronchiolitis in infants less than 1 year of age presenting with a first time episode. Cincinnati Children's Hospital Medical Center. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2006 May.
Website: http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/bronchiolitis.htm

Bibliography

1. American Academy of Pediatrics. Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and Management of Bronchiolitis. Pediatrics. 2006;118:1774-93.
2. Cincinnati Children's Hospital Medical Center. Evidence based clinical practice guideline for medical management of bronchiolitis in infants less than 1 year of age presenting with a first time episode. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2006 May. 13 p.
3. Callen Blecua M, Torregrosa Bertet MJ, Bamonde Rodríguez L y Grupo de Vías Respiratorias. Protocolo de Bronquiolitis Diagnóstico y tratamiento en Atención Primaria. Protocolo del GVR (publicación P-GVR-4) [consultado 15/08/07]. Disponible en: www.aepap.org/gvr/protocolos.htm
4. Scottish Intercollegiate Guidelines Network. Bronquiolitis in children. SIGN publication number 91. 2006, p. 1-41.
5. McConnochie KM. Bronchiolitis: What´s in the name? Am J Dis Child. 1993;137:11-3.
6. López Guinea A, Casado Flores J, Martín Sobrino MA, Espínola Docio B, De la Calle Cabrera T, Serrano A, García Teresa MA. Bronquiolitis grave. Epidemiología y evolución de 284 pacientes. An Pediatr (Barc). 2007;67:116-22.
7. Vicente D, Montes M, Cilla G, Pérez-Trallero E. Hospitalization for respiratory syncytial virus in the paediatric population in Spain. Epidemiol Infect. 2003;131:867-72.
8. Jovell AJ, Aymerich M. Evidència científica i presa de decisions en sanitat. Barcelona. Grupo MSD. 1999;65-105;221-34.
9. Jovell AJ, Navarro Rubio MD. Guías de práctica clínica. FMC. 1995;2:152-5.
10. Grupo de trabajo sobre GPC. Elaboración de Guías de Práctica Clínica en el Sistema Nacional de Salud. Manual Metodológico. Madrid: Plan Nacional para el SNS del MSC; Zaragoza: Instituto Aragonés de Ciencias de la Salud-I+CS, 2007. Guías de Práctica Clínica en el SNS: I+CS. N° 2006/0I. www.guiasalud.es
11. The AGREE Collaboration. AGREE Instrument Spanish version. www.agreecollaboration.org
12. New Zealand Guidelines Group. Wheeze and Chest Infection in Infants under 1 year. April 2005.
13. Etxeberria A, Rotaeche R, Lekue I, Callén B, Merino M, Villar M, et al. Descripción de la metodología de elaboración- adaptación- actualización empleada en la guía de práctica clínica sobre asma de la CAPV. Proyecto de Investigación Comisionada. Vitoria-Gasteiz. Departamento de Sanidad. Gobierno Vasco, 2005. Informe n°: osteba D-05-03.
14. Voets S, van Berlaer G, Hachimi-Idrissi S. Clinical predictors of the severity of bronchiolitis. Eur J Emerg Med. 2006 Jun;13(3):134-8.
15. Koehoorn M, Karr CJ, Demers PA, Lencar C, Tamburic L, Brauer M. Descriptive epidemiological features of bronchiolitis in a population-based cohort. Pediatrics. 2008 Dec;122(6):1196-203.
16. Carroll KN, Gebretsadik T, Griffin MR, Wu P, Dupont WD, Mitchel EF, et al. Increasing burden and risk factors for bronchiolitis-related medical visits in infants enrolled in a state healthcare insurance plan. Pediatrics. 2008 Jul;122(1):58-64.
17. Rossi GA, Medici MC, Arcangeletti MC, Lanari M, Merolla R, Paparatti UD, et al.; Osservatorio RSv Study Group. Risk factors for severe RSV-induced lower respiratory tract infection over four consecutive epidemics. Eur J Pediatr. 2007 Dec;166(12):1267-72. Epub 2007 Feb 17.

18. Figueras Aloy J, López Sastre J, Medrano López C, Bermúdez-Cañete Fernández R, Fernández Pineda L, Bonillo Perales A, et al. Spanish multidisciplinary consensus on the prevention of respiratory syncytial virus infection in children. An Pediatr (Barc). 2008;69(1):63-71.
19. Dornelles CT, Piva JP, Marostica PJ. Nutritional status, breastfeeding, and evolution of Infants with acute viral bronchiolitis. J Health Popul Nutr. 2007 Sep;25(3):336-43.
20. Chatzimichael A, Tsalkidis A, Cassimos D, Gardikis S, Tripsianis G, Deftereos S, et al. The role of breastfeeding and passive smoking on the development of severe bronchiolitis in infants. Minerva Pediatr. 2007 Jun;59(3):199-206.
21. Karr C, Lumley T, Schreuder A, Davis R, Larson T, Ritz B, Kaufman J. Effects of subchronic and chronic exposure to ambient air pollutants on infant bronchiolitis. Am J Epidemiol 2007;165:553-60.
22. Bloemers BL, van Furth AM, Weijerman ME, Gemke RJ, Broers CJ, van den Ende K, et al. Down syndrome: a novel risk factor for respiratory syncytial virus bronchiolitis – a prospective birth-cohort study. Pediatrics. 2007 Oct;120(4):e1076-81.
23. Wilkesmann A, Ammann RA, Schildgen O, Eis-Hübinger AM, Müller A, Seidenberg J, et al.; DSM RSv Ped Study Group. Hospitalized children with respiratory syncytial virus infection and neuromuscular impairment face an increased risk of a complicated course. Pediatr Infect Dis J. 2007 Jun;26(6):485-91.
24. Hon KL, Leung E, Tang J, Chow cm, Leung TF, Cheung KL, Ng PC. Premorbid factors and outcome associated with respiratory virus infections in a pediatric intensive care unit. Pediatr Pulmonol. 2008 Mar;43(3):275-80.
25. Kaplan NM, Dove W, Abd-Eldayem SA, Abu-Zeid AF, Shamoon HE, Hart CA. Molecular epidemiology and disease severity of respiratory syncytial virus in relation to other potential pathogens in children hospitalized with acute respiratory infection in Jordan. J Med virol. 2008 Jan;80(1):168-74.
26. Fodha I, vabret A, Ghedira L, Seboui H, Chouchane S, Dewar J, et al. Respiratory syncytial virus infections in hospitalized infants: association between viral load, virus subgroup, and disease severity. J Med virol. 2007 Dec;79(12):1951-8.
27. Puthothu B, Krueger M, Forster J, Heinze J, Weckmann M, Heinzmann A. Interleukin (IL)-18 polymorphism 133C/G is associated with severe respiratory syncytial virus infection. Pediatr Infect Dis J. 2007 Dec;26(12):1094-8.
28. Liu LL, Gallaher MM, Davis RL, Rutter cm, Lewis TC, Marcuse EK. Use of a respiratory clinical score among different providers. Pediatr Pulmonol. 2004 Mar;37(3):243-8.
29. Beck R, Elias N, Shoval S, Tov N, Talmon G, Godfrey S, Bentur L. Computerized acoustic assessment of treatment efficacy of nebulized epinephrine and albuterol in RSv bronchiolitis. BMC Pediatr. 2007 Jun 2;7:22.
30. Mansbach JM, Clark S, Christopher NC, Lovecchio F, Kunz S, Acholonu U, Camargo CA Jr. Prospective multicenter study of bronchiolitis: predicting safe discharges from the emergency department. Pediatrics. 2008 Apr;121(4):680-8.
31. Lind I, Gill JH, Calabretta N, Polizzoto M. Clinical inquiries. What are hospital admission criteria for infants with bronchiolitis? J Fam Pract. 2006 Jan;55(1):67-9.
32. Walsh P, Rothenberg SJ, o'Doherty S, Hoey H, Healy R. A validated clinical model to predict the need for admission and length of stay in children with acute bronchiolitis. Eur J Emerg Med. 2004 oct;11(5):265-72.
33. Willwerth BM, Harper MB, Greenes DS. Identifying hospitalized infants who have bronchiolitis and are at high risk for apnea. Ann Emerg Med. 2006 oct;48(4):441-7.
34. Welliver RC Sr. Temperature, humidity, and ultraviolet B radiation predict community respiratory syncytial virus activity. Pediatr Infect Dis J. 2007 Nov;26(11 Suppl):S29-35.

35. Mansbach JM, McAdam AJ, Clark S, Hain PD, Flood RG, Acholonu U, Camargo CA Jr. Prospective multicenter study of the viral etiology of bronchiolitis in the emergency department. Acad Emerg Med. 2008 Feb;15(2):111-8.
36. Papadopoulos NG, Moustaki M, Tsolia M, Bossios A, Astra E, Prezerakou A, et al. Association of rhinovirus infection with increased disease severity in acute bronchiolitis. Am J Respir Crit Care Med. 2002 May 1;165(9):1285-9.
37. Jacques J, Bouscambert-Duchamp M, Moret H, Carquin J, Brodard v, Lina B, et al. Association of respiratory picornaviruses with acute bronchiolitis in French infants. J Clin virol. 2006 Apr;35(4):463-6. Epub 2006 Jan 6.
38. Kim YK, Lee HJ. Human metapneumovirus-associated lower respiratory tract infections in Korean infants and young children. Pediatr Infect Dis J. 2005 Dec;24(12):1111-2.
39. Alonso A, Andres JM, Garmendia JR, Diez I, Gil JM, Ardura J. Bronchiolitis due to respiratory syncytial virus in hospitalized children: a study of seasonal rhythm. Acta Paediatr. 2007 May;96(5):731-5. Epub 2007 Mar 23.
40. Bordley WC, Viswanathan M, King VJ, Sutton SF, Jackman AM, Sterling L, Lohr KN. Diagnosis and testing in bronchiolitis: a systematic review. Arch Pediatr Adolesc Med. 2004 Feb;158(2):119-26. Review.
41. Luginbuhl LM, Newman TB, Pantell RH, Finch SA, Wasserman RC. Office-based treatment and outcomes for febrile infants with clinically diagnosed bronchiolitis. Pediatrics. 2008 Nov;122(5):947-54.
42. Bilavsky E, Shouval DS, Yarden-Bilavsky H, Fisch N, Ashkenazi S, Amir J. A prospective study of the risk for serious bacterial infections in hospitalized febrile infants with or without bronchiolitis. Pediatr Infect Dis J. 2008 Mar;27(3):269-70.
43. Purcell K, Fergie J. Lack of usefulness of an abnormal white blood cell count for predicting a concurrent serious bacterial infection in infants and young children hospitalized with respiratory syncytial virus lower respiratory tract infection. Pediatr Infect Dis J. 2007 Apr;26(4):311-5.
44. Andreola B, Bressan S, Callegaro S, Liverani A, Plebani M, Da Dalt L. Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department. Pediatr Infect Dis J. 2007 Aug;26(8):672-7.
45. Maniaci v, Dauber A, Weiss S, Nylen E, Becker KL, Bachur R. Procalcitonin in young febrile infants for the detection of serious bacterial infections. Pediatrics. 2008 oct;122(4):701-10.
46. Martinón-Torres F, Rodríguez-Núñez A, Martinón-Sánchez JM. Nasal continuous positive airway pressure with heliox versus air oxygen in infants with acute bronchiolitis: a crossover study. Pediatrics. 2008 May;121(5):e1190-5. Epub 2008 Apr 14.
47. Bastien N, Chui N, Robinson JL, Lee BE, Dust K, Hart L, Li Y. Detection of human bocavirus in Canadian children in a 1-year study. J Clin Microbiol. 2007 Feb;45(2):610-3. Epub 2006 Nov 22.
48. Jacques J, Moret H, Renois F, Lévêque N, Motte J, Andréoletti L. Human Bocavirus quantitative DNA detection in French children hospitalized for acute bronchiolitis. J Clin virol. 2008;43:142-7.
49. Bosis S, Esposito S, Niesters HG, Zuccotti GV, Marseglia G, Lanari M, et al. Role of respiratory pathogens in infants hospitalized for a first episode of wheezing and their impact on recurrences. Clin Microbiol Infect. 2008 Jul;14(7):677-84.
50. García-García ML, Calvo C, Casas I, Bracamonte T, Rellán A, Gozalo F, et al. Human metapneumovirus bronchiolitis in infancy is an important risk factor for asthma at age 5. Pediatr Pulmonol. 2007;42:458-64.
51. Legoff J, Kara R, Moulin F, Si-Mohamed A, Krivine A, Bélec L, Lebon P. Evaluation of the one-step multiplex real-time reverse transcription-CRP ProFlu-1 assay for detection of influenza A and influenza B viruses and respiratory syncytial viruses in children. J Clin Microbiol. 2008 Feb;46(2):789-91. Epub 2007 Dec 5.

52. Aslanzadeh J, Zheng X, Li H, Tetreault J, Ratkiewicz I, Meng S, et al. Prospective evaluation of rapid antigen tests for diagnosis of respiratory syncytial virus and human metapneumovirus infections. J Clin Microbiol. 2008 May;46(5):1682-5. Epub 2008 Mar 12.
53. Henrickson KJ, Hall CB. Diagnostic assays for respiratory syncytial virus disease. Pediatr Infect Dis J. 2007 Nov;26(11 Suppl):S36-40. Review.
54. Gadomski AM, Bhasale AL. Broncodilatadores para la bronquiolitis (Revisión Cochrane traducida). En: La Biblioteca Cochrane Plus, 2008 Número 1. oxford: Update Software Ltd. Disponible en: http://www.update-software.com (Traducida de The Cochrane Library, 2008 Issue 1. Chichester, UK: John Wiley & Sons, Ltd.)
55. Hartling L, Wiebe N, Russell K, Patel H, Klassen TP. Epinefrina para la bronquiolitis (Revisión Cochrane traducida). En: La Biblioteca Cochrane Plus, 2008 Número 1. Oxford: Update Software Ltd. Disponible en: http://www.update-software.com (Traducida de The Cochrane Library, 2008 Issue 1. Chichester, UK: John Wiley & Sons, Ltd.)
56. Levin DL, Garg A, Hall LJ, Slogic S, Jarvis JD, Leiter JC. A prospective randomized controlled blinded study of three bronchodilators in infants with respiratory syncytial virus bronchiolitis on mechanical ventilation. Pediatr Crit Care Med. 2008 Nov;9(6):598-604.
57. Brooks LJ, Cropp GJ. Theophylline therapy in bronchiolitis. A retrospective study. Am J Dis Child. 1981 oct;135(10):934-6.
58. Ramesh P, Samuels M. Are methylxanthines effective in preventing or reducing apnoeic spells in infants with bronchiolitis? Arch Dis Child. 2005 Mar;90(3):321-2.
59. Sajit NT, Steggall M, Padmakumar B. Apnoeas in bronchiolitis: is there a role for caffeine? Arch Dis Child. 2005 Apr;90(4):438.
60. Boogaard R, Hulsmann AR, van Veen L, Vaessen-Verberne AA, Yap YN, Sprij AJ, et al. Recombinant human deoxyribonuclease in infants with respiratory syncytial virus bronchiolitis. Chest. 2007 Mar;131(3):788-95.
61. Nasr SZ, Strouse PJ, Soskolne E, Maxvold NJ, Garver KA, Rubin BK, Moler FW. Efficacy of recombinant human deoxyribonuclease I in the hospital management of respiratory syncytial virus bronchiolitis. Chest. 2001 Jul;120(1):203-8.
62. Merkus PJ, de Hoog M, van Gent R, de Jongste JC. DNase treatment for atelectasis in infants with severe respiratory syncytial virus bronchiolitis. Eur Respir J. 2001 oct;18(4):734-7.
63. Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulized hypertonic saline solution for acute bronchiolitis in infants. Cochrane Database Syst Rev. 2008 oct 8;(4):CD006458. Review.
64. Ralston S, Roohi M. A Randomized, Controlled Trial of Nasal Phenylephrine in Infants Hospitalized for Bronchiolitis. J Pediatr 2008;153:795-8.
65. FDA MedWatch Safety Alert. Cough and Cold Medications in Children Less Than Two Years of Age. January 17, 2008. Disponible en: http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough
66. Ventre K, Haroon M, Davison C. Surfactant therapy for bronchiolitis in critically ill infants. Cochrane Database Syst Rev. 2006 Jul 19;3:CD005150. Review.
67. Bar A, Srugo I, Amirav I, Tzverling C, Naftali G, Kugelman A. Inhaled furosemide in hospitalized infants with viral bronchiolitis: a randomized, double-blind, placebo-controlled pilot study. Pediatr Pulmonol. 2008;43:261-7.
68. Spurling GK, Fonseka K, Doust J, Del Mar C. Antibiotics for bronchiolitis in children. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD005189. Review.
69. Kneyber MC, van Woensel JB, Uijtendaal E, Uiterwaal CS, Kimpen JL; Dutch Antibiotics in RSv Trial (DART) Research Group. Azithromycin does not improve disease course in hospitalized infants with respiratory syncytial virus (RSV) lower respiratory tract disease: a randomized equivalence trial. Pediatr Pulmonol. 2008 Feb;43(2):142-9.
70. Tahan F, ozcan A, Koc N. Clarithromycin in the treatment of RSv bronchiolitis: a double-blind, randomised, placebo-controlled trial. Eur Respir J. 2007 Jan;29(1):91-7. Epub 2006 Oct 18.

71. Martinón-Torres F, Rodríguez-Núñez A, Martinón-Sánchez JM. Heliox therapy in infants with acute bronchiolitis. Pediatrics. 2002 Jan;109(1):68-73.
72. Iglesias Fernández C, López-Herce Cid J, Mencía Bartolomé S, Santiago Lozano MJ, Moral Torrero R, Carrillo Alvarez A. Eficacia del tratamiento con heliox en niños con insuficiencia respiratoria. An Pediatr (Barc). 2007;66(3):240-7.
73. Martinón-Torres F, Rodríguez-Núñez A, Martinón-Sánchez JM. Nasal continuous positive airway pressure with heliox in infants with acute bronchiolitis. Respir Med. 2006 Aug;100(8):1458-62. Epub 2006 Jan 10.
74. Cambonie G, Milési C, Jaber S, Amsallem F, Barbotte E, Picaud JC, Matecki S. Nasal continuous positive airway pressure decreases respiratory muscles overload in young infants with severe acute viral bronchiolitis. Intensive Care Med. 2008 oct;34(10):1865-72. Epub 2008 Jul 8.
75. Liet JM, Millotte B, Tucci M, Laflammme S, Hutchison J, Creery D, et al.; Canadian Critical Care Trials Group. Noninvasive therapy with heliox-oxygen for severe bronchiolitis. J Pediatr. 2005 Dec;147(6):812-7.
76. Garner SS, Wiest DB, Stevens CE, Habib DM. Effect of heliox on albuterol delivery by metered-dose inhaler in pediatric in vitro models of mechanical ventilation. Pharmacotherapy. 2006 oct;26(10):1396-402.
77. Hess DR, Acosta FL, Ritz RH, Kacmarek RM, Camargo CA Jr.The effect of heliox on nebulizer function using a beta-agonist bronchodilator. Chest. 1999 Jan;115(1):184-9.
78. Kim K, Phrampus E, venkataraman S, Pitetti R, Saville A, Corcoran T, Gracely E, Funt N and Thompson A. Heliox/oxygen-Driven Albuterol Nebulization in the Treatment of Children With Moderate to Severe Asthma Exacerbations: A Randomized, Controlled Trial. Pediatrics 2005;116;1127-1133.
79. Blom D, Ermers M, Bont L, van Aalderen WM, van Woensel JB. Inhaled corticosteroids during acute bronchiolitis in the prevention of post-bronchiolitic wheezing. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD004881.
80. Patel H, Platt R, Lozano JM, Wang EE. Glucocorticoids for acute viral bronchiolitis in infants and young children. Cochrane Database Syst Rev. 2004;(3):CD004878. Review. Update in: Cochrane Database Syst Rev. 2008;(1):CD004878.
81. Corneli HM, Zorc JJ, Mahajan P, Shaw KN, Holubkov R, Reeves SD, et al.; Bronchiolitis Study Group of the Pediatric Emergency Care Applied Research Network (PECARN). A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. N Engl J Med. 2007 Jul 26;357(4):331-9. Fe de erratas en: N Engl J Med. 2008 Oct 30;359(18):1972.
82. Lehtinen P, Ruohola A, vanto T, vuorinen T, Ruuskanen O, Jartti T. Prednisolone reduces recurrent wheezing after a first wheezing episode associated with rhinovirus infection or eczema. J Allergy Clin Immunol. 2007 Mar;119(3):570-5. Epub 2006 Dec 27.
83. Plint AC, Johnson DW, Patel H, Wiebe N, Correll R, Brant R, et al.; Pediatric Emergency Research Canada (PERC). Epinephrine and dexamethasone in children with bronchiolitis. N Engl J Med. 2009 May 14;360(20):2079-89.
84. Buckingham SC, Jafri HS, Bush AJ, Carubelli cm, Sheeran P, Hardy RD, et al. A randomized, double-blind, placebo-controlled trial of dexamethasone in severe respiratory syncytial virus (RSv) infection: effects on RSv quantity and clinical outcome. J Infect Dis. 2002 May 1;185(9):1222-8. Epub 2002 Apr 16.
85. van Woensel JB, van Aalderen WM, de Weerd W, Jansen NJ, van Gestel JP, Markhorst DG, et al. Dexamethasone for treatment of patients mechanically ventilated for lower respiratory tract infection caused by respiratory syncytial virus. Thorax. 2003 May;58(5):383-7.
86. Ventre K, Randolph AG Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. Cochrane Database Syst Rev. 2007 Jan 24;(1): CD000181. Review.

87. Chen CH, Lin YT, Yang YH, Wang LC, Lee JH, Kao CL, Chiang BL. Ribavirin for respiratory syncytial virus bronchiolitis reduced the risk of asthma and allergen sensitization. Pediatr Allergy Immunol. 2008 Mar;19(2):166-72.
88. Chávez-Bueno S, Mejías A, Merryman RA, Ahmad N, Jafri HS, Ramilo O. Intravenous palivizumab and ribavirin combination for respiratory syncytial virus disease in high-risk pediatric patients. Pediatr Infect Dis J. 2007 Dec;26(12):1089-93.
89. Bisgaard H; Study Group on Montelukast and Respiratory Syncytial virus. A randomized trial of montelukast in respiratory syncytial virus postbronchiolitis. Am J Respir Crit Care Med. 2003 Feb 1;167(3):379-83. Epub 2002 Oct 3.
90. Bisgaard H, Flores-Nunez A, Goh A, Azimi P, Halkas A, Malice MP, et al. Study of montelukast for the treatment of respiratory symptoms of post-respiratory syncytial virus bronchiolitis in children. Am J Respir Crit Care Med. 2008 Oct 15;178(8):854-60. Epub 2008 Jun 26.
91. Amirav I, Luder AS, Kruger N, Borovitch Y, Babai I, Miron D, et al. A double-blind, placebo-controlled, randomized trial of montelukast for acute bronchiolitis. Pediatrics. 2008 Dec;122(6): e1249-55. Epub 2008 Nov 4.
92. Khoshoo V, Ross G, Kelly B, Edell D, Brown S. Benefits of thickened feeds in previously healthy infants with respiratory syncytial viral bronchiolitis. Pediatr Pulmonol. 2001 Apr;31(4):301-2.
93. Perrotta C, Ortiz Z, Roque M. Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD004873. Review.
94. Postiaux G. Des techniques expiratoires lentes pour l'épuration des voies aériennes distales. Ann Kinésithér. 1997;24(4):166-77.
95. Larrar S, Essouri S, Durand P, Chevret L, Haas v, Chabernaud JL, et al. Effects of nasal continuous positive airway pressure ventilation in infants with severe acute bronchiolitis. Arch Pediatr. 2006 Nov;13(11):1397-403. Epub 2006 Sep 7. French.
96. Mayordomo-Colunga J, Medina A, Rey C, Los Arcos M, Concha A, Menéndez S. Predictores de éxito y de fracas en la ventilación no invasive en la bronquiolitis aguda. An Pediatr (Barc). 2009 Jan;70(1):34-9. Epub 2008 Dec 3.
97. Thia LP, McKenzie SA, Blyth TP, Minasian CC, Kozlowska WJ, Carr SB. Randomised controlled trial of nasal continuous positive airways pressure (CPAP) in bronchiolitis. Arch Dis Child. 2008 Jan;93(1):45-7. Epub 2007 Mar 7.
98. Campion A, Huvenne H, Leteurtre S, Noizet O, Binoche A, Diependaele JF, et al. Non-invasive ventilation in infants with severe infection presumably due to respiratory syncytial virus: feasibility and failure criteria. Arch Pediatr. 2006 Nov;13(11):1404-9. Epub 2006 Sep 15.
99. Berner ME, Hanquinet S, Rimensberger PC. High frequency oscillatory ventilation for respiratory failure due to RSv bronchiolitis. Intensive Care Med. 2008 Sep;34(9):1698-702. Epub 2008 May 24.
100. Unger S, Cunningham S. Effect of oxygen supplementation on length of stay for infants hospitalized with acute viral bronchiolitis. Pediatrics. 2008 Mar;121(3):470-5.
101. Simpson H, Matthew DJ, Habel AH, George EL. Acute respiratory failure in bronchiolitis and pneumonia in infancy. Modes of presentation and treatment. Br Med J. 1974 Jun 22;2(5920):632-6.
102. American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Pediatrics. 2003 Dec;112(6 Pt 1):1442-6.
103. Fuller H, Del Mar C. Immunoglobulin treatment for respiratory syncytial virus infection. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD004883.
104. Frogel M, Nerwen C, Boron M, Cohen A, VanVeldhuisen P, Harrington M, Groothuis J. Palivizumab Outcomes Registry Group. Improved outcomes with home-ba-sed administration

of palivizumab: results from the 2000-2004 Palivizumab Outcomes Registry. Pediatr Infect Dis J. 2008 Oct;27(10):870-3.

105. Figueras J, Quero J, Comisión de Estándares de la Sociedad Española de Neonatología. Recomendaciones para la prevención de la infección por virus respiratorio sincitial. An Pediatr (Barc). 2005 Oct;63(4):357-62.

106. Kamal-Bahl S, Doshi J, Campbell J. Economic analyses of respiratory syncytial virus immunoprophylaxis in high-risk infants: a systematic review. Arch Pediatr Adolesc Med. 2002 Oct;156(10):1034-41.

107. Simpson S, Burls A. A systematic review of the effectiveness and cost-effectiveness of palivizumab (Synagis®) in the prevention of respiratory syncytial virus (RSv) infection in infants at high risk of infection. A West Midlands Development and Evaluation Service Report. ISBN No. 0704423219.

108. Wang D, Cummins C, Bayliss S, Sandercock J, Burls A. Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation. Health Technol Assess. 2008 Dec;12(36):iii, ix-x, 1-86.

109. Austin J. Preventing respiratory syncytial virus in homebound premature infants. Home Healthc Nurse. 2007 Jul-Aug;25(7):429-32.

110. Harris JA, Huskins WC, Langley JM, Siegel JD; Pediatric Special Interest Group of the Society for Healthcare Epidemiology of America. Healthcare epidemiology perspective on the October 2006 recommendations of the Subcommittee on Diagnosis and Management of Bronchiolitis. Pediatrics. 2007 Oct;120(4):890-2.

111. Simon A, Khurana K, Wilkesmann A, Müller A, Engelhart S, Exner M, et al. Nosocomial respiratory syncytial virus infection: impact of prospective surveillance and targeted infection control. Int J Hyg Environ Health. 2006 Jul;209(4):317-24. Epub 2006 May 11.

112. Kurz H, Herbich K, Janata O, Sterniste W, Bauer K. Experience with the use of palivizumab together with infection control measures to prevent respiratory syncytial virus outbreaks in neonatal intensive care units. J Hosp Infect. 2008 Nov;70(3):246-52.

113. Groothuis J, Bauman J, Malinoski F, Eggleston M. Strategies for prevention of RSV nosocomial infection. J Perinatol. 2008 May;28(5):319-23. Epub 2008 Mar 27.

114. Regamey N, Kaiser L, Roiha HL, Deffernez C, Kuehni CE, Latzin P, et al; Swiss Paediatric Respiratory Research Group. Viral etiology of acute respiratory infections with cough in infancy: a community-based birth cohort study. Pediatr Infect Dis J. 2008 Feb;27(2):100-5.

115. Koehoorn M, Karr CJ, Demers PA, Lencar C, Tamburic L, Brauer M. Descriptive epidemiological features of bronchiolitis in a population-based cohort. Pediatrics. 2008 Dec;122(6):1196-203.

116. Pérez-Yarza EG, Moreno A, Lázaro P, Mejías A, Ramilo O. The association between respiratory syncytial virus infection and the development of childhood asthma: a systematic review of the literature. Pediatr Infect Dis J. 2007 Aug;26(8):733-9.

117. Hyvärinen MK, Kotaniemi-Syrjänen A, Reijonen TM, Korhonen K, Korppi MO. Lung function and bronchial hyper-responsiveness 11 years after hospitalization for bronchiolitis. Acta Paediatr. 2007 Oct;96(10):1464-9.

118. Wu P, Dupont WD, Griffin MR, Carroll KN, Mitchel EF, Gebretsadik T, Hartert TV. Evidence of a causal role of winter virus infection during infancy in early childhood asthma. Am J Respir Crit Care Med. 2008 Dec 1;178(11):1123-9. Epub 2008 Sep 5.

119. Wenzel SE, Gibbs RL, Lehr MV, Simoes EA. Respiratory outcomes in high-risk children 7 to 10 years after prophylaxis with respiratory syncytial virus immune globulin. Am J Med. 2002 Jun 1;112(8):627-33.

120. Simoes EA, Groothuis JR, Carbonell-Estrany X, Rieger CH, Mitchell I, Fredrick LM, Kimpen JL. Palivizumab Long-Term Respiratory Outcomes Study Group. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. J Pediatr. 2007 Jul;151(1):34-42, 42.e1.

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