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Abstract:

Bronchiolitis is the number one cause of hospitalization in infants during the first year of life. Clinical guidelines recommend primarily supportive care and discourage use of pharmacotherapies and diagnostics. However, there continues to be widespread use of non-recommended therapies and variation in the use of therapeutic interventions among hospitals in the United States. Here we review evidence-based management of this common disease in order to optimize resource utilization, decrease healthcare costs, and decrease unnecessary hospitalization. Current evidence does not support the routine use of chest radiographs, viral testing or laboratory evaluation in children with bronchiolitis. In addition, routine administration of bronchodilators, including albuterol and nebulized epinephrine, corticosteroids and hypertonic saline are not recommended for infants and children with bronchiolitis. Intravenous or nasogastric hydration and nutritional support, supplemental oxygen, and respiratory support are recommended. Standardization of bronchiolitis care with evidence based institutional clinical pathways spanning ED to inpatient care can help optimize resource utilization while simultaneously improving care of bronchiolitis and reducing hospital length of stays and costs.

Keywords:

Bronchiolitis; albuterol; epinephrine; supportive care

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Improving Evidence Based Bronchiolitis Care

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Bronchiolitis is the number one cause of hospitalization in infants during the first 12 months of life resulting in approximately 100,000 hospital admissions annually.[1,2] In the United States this translates to an estimated cost of $1.73 billion and direct medical costs exceeding $500 million.[2] Clinical guidelines recommend primarily supportive care and discourage the use of pharmacotherapies and diagnostics as they do not improve outcomes.[3-9] However, there continues to be wide variability in hospital-based care for bronchiolitis both among US and international institutions.[2,10,11] Given the high financial and medical burden of bronchiolitis on families and healthcare facilities, it is prudent to continue reviewing evidence based management of this common disease in order to optimize resource utilization, decrease healthcare costs, and decrease unnecessary hospitalization.[11,12]

BACKGROUND

Pathogenesis

Bronchiolitis is a viral illness occurring in children under age 2 years characterized by an upper respiratory prodrome followed by a lower respiratory tract infection. The virus infects the terminal bronchiolar epithelium cells causing edema, excessive mucous, and epithelial sloughing resulting in obstruction and atelectasis of the small airways. Virus induced wheezing or acute viral-triggered asthma may overlap with the clinical syndrome of bronchiolitis in young children.

Virology & Epidemiology

The incidence of bronchiolitis is typically highest between November and March with regional variations.[7] Multiple viruses infect the lower respiratory tract causing the clinical syndrome

of bronchiolitis. Respiratory syncytial virus (RSV) is by far the most common etiology and is responsible for over 70% of bronchiolitis cases.[13] By age 2 years 90% of children have been infected with RSV, and 40% will contract a lower respiratory tract infection.[14,15] Reinfection with RSV is common since a primary infection does not confer any immunity.[16] Rhinovirus is the second most common viral pathogen causing bronchiolitis and is associated with recurrent wheezing.[13] Other less common etiologies include influenza, human metapneumovirus, coronavirus, parainfluenza, adenovirus, and human bocavirus.[13,17] One third of children hospitalized with bronchiolitis will have co-infection with two or more viruses.[18]

Risk Factors For Severe Disease

Risk factors for complications and severe disease include age less than 12 weeks, prematurity (gestational age < 36 weeks), underlying hemodynamically significant cardio-pulmonary disease, immunodeficiency, anatomic defects of the airway, and neurologic disease.[14,19]

CLINICAL PRESENTATION & DIAGNOSIS

Infants and young children with bronchiolitis typically present with a prodrome of fever, cough, congestion, and rhinorrhea followed by lower respiratory tract involvement. Lower respiratory tract involvement manifests as tachypnea, wheezing, rales, and increased respiratory effort evidenced by retractions, nasal flaring, accessory muscle use, and grunting. The diagnosis of bronchiolitis should be based primarily on history and physical presentation and should not routinely include imaging or lab diagnostics.[7]

Persistent increased respiratory effort, severe tachypnea, hypoxemia, apnea, or intolerance of feeds may warrant hospitalization.[20,21] Assessing severity for management decisions is complicated by the variability in exam findings over time. Evidence relating specific clinical finding with outcomes is limited.[22] There have been many attempts to create an objective clinical scoring system for severity assessment based on clinical evaluation, but there has been no widespread adoption of any one system due to the lack of validated predictive value.[23]

In addition to known risk factors for severe disease, the effects of the respiratory symptoms on feeding, hydration, and mental status should also be assessed when considering hospitalization.

Chest Radiographs

Current evidence does not support the routine use of chest radiographs in children with bronchiolitis. They are not needed to diagnose bronchiolitis, do not alter the clinical course, and can lead to unnecessary antibiotic use. Chest radiographs should be reserved for patients in whom the physical exam findings suggest an alternative diagnosis (concern for foreign body, vascular ring, undiagnosed cardiac disease, etc.) or presentation is particularly severe.[7,24]

Features of bronchiolitis on chest radiograph are nonspecific, often with patchy or segmental atelectasis and peribronchial thickening. These findings can often be interpreted as developing pneumonia leading to unnecessary antibiotic use, particularly for patients with mild to moderate disease.[7,24] In a nine year prospective study of 565 children hospitalized with RSV only 0.9 percent developed subsequent bacterial pneumonia.[25] Obtaining chest radiographs is warranted in those presenting with severe disease requiring intensive care unit (ICU) admission or mechanical ventilation. These patients are at increased risk for developing complications such as secondary bacterial pneumonia, pneumomediastinum, and pneumothorax.[26]

Laboratory Diagnostics

Viral polymerase chain reaction (PCR) testing is not routinely recommended. There is no clear benefit to determining the exact viral etiology by PCR in a patient with known bronchiolitis.[18] There may be some potential benefit of a viral PCR in an unclear clinical picture or severe presentation where multiple diagnoses are being considered. If a child receiving monthly prophylaxis with palivizumab presents with bronchiolitis, viral PCR should be performed to determine if RSV is the etiological agent. A positive RSV finding warrants discontinuation of the prophylaxis given the low likelihood of repeat infection with RSV in the same year.[7]

Secondary bacterial infections are uncommon in children with bronchiolitis, with the exception of acute otitis media. One nine year prospective study involving 565 patients with RSV bronchiolitis demonstrated subsequent bacterial infection of any kind in only 1.2%.[25] Other studies have shown that in febrile infants with a distinct viral syndrome (i.e. bronchiolitis) the risk of a secondary bacterial infection in the blood or cerebrospinal fluid (CSF) is less than 1 percent.[8] A systemic review of serious bacterial infections in febrile hospitalized infants age 30-90 days confirmed the extreme rarity of bacteremia and CSF infections and found the rate of

urinary tract infection to be 1%.[27] These findings are supported by other prospective studies suggesting that routine evaluation for serious bacterial infection (complete blood count, urinalysis, urine culture, blood culture, CSF studies) in febrile infants age 30-90 days with a diagnosis of bronchiolitis is unjustified.[7,28,29]

EVIDENCE BASED SUPPORTIVE THERAPIES

The American Academy of Pediatrics (AAP), along with multiple similar international groups, recommends using evidence based supportive therapies to manage bronchiolitis.[4,7,9,11] These include intravenous (IV) or nasogastric (NG) hydration and nutritional support, supplemental oxygen, and respiratory support (Table 1).

Hydration

Infants and young children with bronchiolitis can have increased insensible losses from fever and tachypnea as well as decreased intake due to congestion, tachypnea, and respiratory distress. Respiratory rates exceeding 60-70 breaths per minute with worsening signs of respiratory distress while feeding (retractions, nasal flaring) may increase the risk of aspiration. If oral hydration cannot be maintained due to tachypnea and increased work of breathing, then IV or NG fluids should be administered.[7]

There is no significant difference in efficacy, safety (including adverse events, ICU admissions, or need for mechanical ventilation), or hospital length of stay (LOS) between infants given intravenous hydration compared to nasogastric hydration.[30] However, infants with moderate to severe respiratory distress (respiratory rate >70, global retractions, cyanosis, apnea) and those requiring mechanical ventilation may benefit from exclusive parental hydration.[7]

Respiratory support is a mainstay of bronchiolitis management and may include nasal suctioning, supplemental oxygen, high flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), and mechanical ventilation.

TABLE 1 Recommended supportive therapies and non-recommended pharmacotherapies in bronchiolitis.

Recommended Supportive Therapies	Non-Recommended Pharmacotherapies
Non-invasive nasal suctioning	Nebulized albuterol
Intravenous or nasogastric hydration & nutrition	Nebulized epinephrine
Supplemental oxygen	Hypertonic saline
Respiratory support (HFNC, CPAP/BiPAP, MV)	Corticosteroids

Nasal Suctioning

Suctioning of the nasopharynx with saline in infants with bronchiolitis is a common practice to improve upper airway obstruction caused by nasal congestion and thus improve the infant's ability to feed. In a retrospective cohort study of 740 infants age 2-12 months hospitalized with bronchiolitis, deep nasal suctioning with a catheter was actually associated with longer hospital LOS, possibly due to trauma and mucosal edema.[31] Interestingly, the same study noted longer LOS when greater than 4 hours lapsed between non-invasive external nasal suctioning. Current data suggest that while frequent non-invasive nasal suctioning is beneficial in the clinical course of bronchiolitis, routine "deep" suctioning with a nasopharyngeal catheter may not be beneficial.[7,31] Frequent catheter suctioning of infants deemed more severe on presentation may be a confounder. Future prospective randomized trials on nasal suctioning may help clarify the data.

Oxygen Support

Supplemental oxygen via nasal cannula should be used in infants and young children unable to maintain oxyhemoglobin saturations above 90% in the setting of bronchiolitis.[7] Pulse oximeter (SpO_2) accuracy in reflecting arterial partial pressure of oxygen (SaO_2) is poor below 90% but accurate within 1% of SaO_2 when reading above 90%.[32] Based on the oxyhemoglobin dissociation curve, when SpO_2 is less than 90% incremental increases in SaO_2 are associated with significant improvement in SpO_2. But when SpO_2 is greater than 90% any further increases requires much larger elevations in SaO_2.

Despite being a poor predictor of respiratory distress, oxygen saturation is a driving clinical factor for hospital admission from the ED and subsequent hospital LOS.[20,33] It is important to weigh the risk of hypoxemia against the risk of a hospitalization. Transient hypoxemia is common in healthy infants.[34] Though chronic hypoxemia is associated with developmental and behavioral problems, these same issues have not been borne out in otherwise healthy children who experience intermittent hypoxemia from temporary disease states.[35]

Carbon dioxide concentrations in the blood have a greater impact on the respiratory drive than oxygen saturations.[7] Respiratory distress is poorly correlated with oxygen saturation in infants and cyanosis is the only clinical sign that accurately identifies hypoxemia in infants and children.[36] Consider discharge home with close follow up, for children with SpO_2 90-92% presenting with mild to moderate disease who are vigorous and maintaining oral hydration with minimal signs of respiratory distress.

Respiratory Support

Children with worsening respiratory distress progressing to respiratory failure benefit from non-invasive ventilation. HFNC and CPAP are both used to mitigate respiratory effort, improve gas exchange, and avoid intubation in the deteriorating child with bronchiolitis.[37,38] Avoiding the possible adverse effects of intubation (laryngeal nerve injury, subglottic stenosis, ventilator associated pneumonia, narcotic withdrawal from sedation) is a clear benefit. HFNC is typically utilized first, followed by CPAP, in attempts to avoid intubation.

HFNC can provide a combination of FiO_2 and positive end expiratory pressure (2-5 cm H_20 with flow 6L).[38] It has been shown to reduce respiratory effort, and a recent prospective study looking at optimal flow rates demonstrated significant improvement in respiratory effort of children with bronchiolitis on 1.5-2 L/kg/minute of HFNC, especially in infants 8 kg.[39]

HFNC also improves gas exchange by washing out CO_2 from pulmonary dead space and decreasing rates of intubation and mechanical ventilation.[38-40] A particularly strong retrospective study in Australia evaluated 330 infants with bronchiolitis and showed a decrease in intubation rates from 37% to 7% after the introduction of HFNC.[41] HFNC was associated with avoidance of ICU admission in a recent randomized trial of 200 children under the age of 2 years of age with moderate severe bronchiolitis who received either early initiation of HFNC or nasal cannula.[42] Early initiation of HFNC was also found to be important in an observational study that revealed an association between HFNC failure and low pretreatment pH and high pretreatment pCO_2.[43]

Infants with persistently severe or worsening respiratory status despite HFNC or CPAP may require intubation and mechanical ventilation. Signs of impending respiratory failure include marked global retractions, nasal flaring, head bobbing, diminished or absent breath sounds, fatigue, bradypnea, hypoxemia despite supplemental oxygen, weak cry and decreased responsiveness to stimulation. Hypercapnea is typically present on blood gas. This information should be utilized in conjunction with the rest of the clinical picture when deciding whether to intubate an infant with bronchiolitis.

Despite the evidence for supportive therapies as the mainstay in bronchiolitis management and the routine recommendation for their use by major US and international guidelines,[4,7,9,11] there continues to be significant inter-hospital and international variation in treatment. A timely study by the Pediatric Emergency Research Networks (PERN) on this very matter demonstrates that 30% of infants hospitalized with bronchiolitis did not receive any evidence based supportive therapies during their emergency department visit or inpatient hospitalization.[11]

PHARMACOLOGIC THERAPIES NOT ROUTINELY RECOMMENDED

The most recent guidelines regarding bronchiolitis management, including AAP Clinical Guidelines (2014), National Institute for Health and Care Excellence (2015), and the Scottish Intercollegiate Guidelines Network (2006), all strongly recommend against the routine administration of bronchodilators for infants and children with bronchiolitis.[7,11] (Figure 1)

Consistent clinical benefit has not been shown with the use of - or -adrenergic agents in randomized controlled studies. While bronchodilators may improve clinical symptom scores in the short-term, they do not improve overall outcomes, the need for hospitalization, or hospital LOS.[7,44-46] Moreover, clinical symptoms scores are not validated measures of efficacy, do not correlate with objective measures (pulmonary function tests) and are subject to inter-use variability.[7]

Albuterol

A Cochrane systematic review of albuterol use in bronchiolitis demonstrated potential adverse effects and increased cost of care without any clear clinical benefit.[5] The review assessed bronchodilator use on oxygen saturations in 30 randomized controlled trials including 2000 children in 12 countries. The heterogeneity of the studies was significantly reduced by sensitivity analysis. Overall, the review showed no benefit, and those studies that did show benefit had weaker methodology and included older children with history of recurrent wheeze.

Logical arguments have been made that there are subsets of infants and children (ie. those with recurrent wheeze and history of eczema) with bronchiolitis who may have reversible airway obstruction from smooth muscle constriction that would benefit from albuterol. A Cochrane review by Chavesse et al on albuterol use in children younger than 2 years with recurrent wheeze did not find any clear benefit from -agonist use in this population subset.[47] The review included studies from the outpatient setting, ED, and pulmonary function lab setting.

Nebulized Epinephrine

The current evidence regarding nebulized epinephrine suggests it should not be used for bronchiolitis in the inpatient setting. A meta-analysis by Hartling et al reviewed the evidence on nebulized epinephrine use for bronchiolitis and found no evidence to support its use inpatient.[44] Several multicenter randomized trials compared nebulized epinephrine to placebo and albuterol and to placebo alone and found a lack of efficacy, while further demonstrating longer LOS if used on a fixed schedule.

The role of nebulized epinephrine in the ED and outpatient setting is unclear. The Canadian Bronchiolitis Epinephrine Steroid Trial,[46] a multicenter randomized trial involving 800 patients from 8 EDs, compared hospitalizations over a 7-day period. After adjusting for multiple variables, there was no change in need for admission by day 7 in the group of patients receiving nebulized epinephrine plus oral dexamethasone compared to the group receiving nebulized placebo plus oral placebo. Additionally, the Hartling et al systemic review of bronchodilators found nebulized epinephrine use in the ED decreased hospital admission on the day of the visit compared to placebo but did not decrease overall admission rates.[44]

Unlike albuterol, nebulized epinephrine cannot be administered at home. It has a transient effect with no significant decrease in progression of illness and subsequent admission rates. Limited evidence does not support routine use of nebulized epinephrine in the ED setting when the plan is to discharge the patient home. However, these trials did not include children with severe disease or respiratory failure making it difficult to generalize the recommendations against bronchodilator use to those specific clinical scenarios. Recent studies show administration of bronchodilators in the ED increased with increasing age (increased likelihood of presenting with recurrent wheezing), decreasing oxygen saturation, increasing respiratory rate, and worsening retractions.[11] A trial of albuterol or nebulized epinephrine as a rescue agent in severe disease may be warranted.[7] Further studies evaluating the use and effect of bronchodilators administered for this purpose are needed.

The recent PERN Study (2017) suggests there has been a decrease in the use of non-recommended interventions.[11] Rates of bronchodilator use have declined from 90%, in 2007-2012 to 25% and rates of chest radiographs have declined from 52-85% to 10-35%.[48] However, there still remain significantly high rates of use of non-recommended therapies and wide variation in the use of therapeutic interventions among hospitals in the US.[48] The PERN study highlights this same variation on an international scale confirming that location of care, regardless of disease severity, is the main predictor of bronchiolitis management.[11]

The current guidelines and recent findings highlight the importance of standardizing acute care of bronchiolitis with evidence based point-of-care clinical practice pathways for ED physicians combined with multidisciplinary institutional pathways.[11] Adherence to standardized clinical practice pathways and guidelines is associated with reduced LOS and healthcare costs.[49]

Corticosteroids

The strongest evidence based recommendation in the most recent AAP Clinical Practice Guidelines recommends against the use of corticosteroids in children with bronchiolitis in any setting.[7] A 2013 Cochrane review of 17 trials (including 2 large ED-based randomized trials) with 2596 patients showed no significant reduction in hospital admissions or LOS with corticosteroids compared to placebo.[3] Even in young children with virus-associated wheezing, randomized controlled trials have not shown oral steroids to be beneficial.[46] Furthermore, an observational study of almost 2500 patients

TABLE 2 Recommendations for palivizumab administration.

Palivizumab Administration Recommendations
Infants born before 29 weeks and 0 days
Infants with hemodynamically significant congenital heart disease
Infants with CLD requiring >21% FiO_2 for at least 28 days after birth
Infants 12-24 months with CLD still requiring O_2, diuretics, or chronic steroids

under age 2 with a previous admission for bronchiolitis and subsequent admission for asthma did not find corticosteroid use during the admission for bronchiolitis to be associated with improved outcomes.[50]

Hypertonic Saline

Theoretically hypertonic saline increases mucociliary clearance and rehydrates the airway surface liquid.[51] However, a 2013 Cochrane review of 11 trials in both inpatient and ED settings showed a small improvement in LOS but no effect on hospitalization rates from the ED with 3% hypertonic saline use.[52] Subsequent well-designed randomized trials reiterate the lack of effect on hospitalization rates but fail to show any improvement in hospital LOS.[7,53] Current evidence does not support the use of hypertonic saline for bronchiolitis in the ED or inpatient settings.

PREVENTION

Palivizumab is a monoclonal antibody against the RSV F glycoprotein used as immunoprophylaxis to decrease the risk of hospitalization due to severe RSV illness in preterm infants (infants born at or before 28 weeks 6 days), those with hemodynamically significant congenital heart disease (most effective in preventing hospitalization in those with acyanotic lesions), and those with chronic lung disease.[54] (Table 2) Prophylaxis consists of a maximum of 5 monthly doses (15 mg/kg/dose) from the start of RSV season.[7]

Primary Prevention

Caregiver and healthcare provider hand washing before and after contact with young children with bronchiolitis, avoiding contact with others with respiratory illnesses, avoiding cigarette smoke exposure, and encouraging breast feeding until at least 6 months of age have all been shown to reduce the spread or decrease the occurrence and severity of bronchiolitis.[7]

SUMMARY

The current evidence and guidelines, both in the US and internationally, recommend supportive therapies including non-invasive nasal suctioning, IV or NG fluid hydration, oxygen support, and respiratory support for management of bronchiolitis in both the inpatient and outpatient or ED settings. Randomized controlled trials, meta-analyses, and systemic reviews do not support the use of diagnostic studies (chest radiographs and viral PCRs) or pharmacotherapies (albuterol, nebulized epinephrine, corticosteroids, and nebulized hypertonic saline), and these interventions are not routinely recommended. Standardization of bronchiolitis care with evidence based institutional clinical pathways spanning ED to inpatient care could help optimize resources while simultaneously improving care of bronchiolitis and reducing hospital LOS and costs.

REFERENCES

1. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med 2009;360:588-98.
2. Hasegawa K, Tsugawa Y, Brown DF, et al. Trends in bronchiolitis hospitalizations in the United States, 2000-2009. Pediatrics 2013;132:28-36.
3. Fernandes RM, Bialy LM, Vandermeer B, et al. Glucocorticoids for acute viral bronchiolitis in infants and young children. Cochrane Database Syst Rev 2013;CD004878 2-5; 9-26.
4. Friedman JN, Rieder MJ, Walton JM, et al. Bronchiolitis: recommendations for diagnosis, monitoring and management of children one to 24 months of age. Paediatr Child Health 2014;19:485-98.
5. Gadomski AM, Scribani MB. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev 2014;CD001266 1-3; 7-14.
6. Hartling L, Bialy LM, Vandermeer B, et al. Epinephrine for bronchiolitis. Cochrane Database Syst Rev 2011:134 CD003123.
7. Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. Pediatrics 2014;134:e1474-502.
8. Spurling GK, Doust J, Del Mar CB, et al. Antibiotics for bronchiolitis in children. Cochrane Database Syst Rev 2011: 1-42 [CD005189].
9. Turner T, Wilkinson F, Harris C, et al. Evidence based guideline for the management of bronchiolitis. Aust Fam Physician 2008;37:6-13.
10. Mittal V, Hall M, Morse R, et al. Impact of inpatient bronchiolitis clinical practice guideline implementation on testing and treatment. J Pediatr 2014;165:570-6.
11. Schuh S, Babl FE, Balziel SR, et al. Practice variation in acute bronchiolitis: a Pediatric Emergency Research Networks study. Pediatrics 2017;140e20170842, https://doi.org/10.1542/peds.2017-0842 [http://pediatrics.aappublications.org/content/early/2017/11/24/peds.2017-0842].
12. Wennberg JE. Unwarranted variations in healthcare delivery: implications for academic medical centres. BMJ 2002;325: 961-4.
13. Mansbach JM, McAdam AJ, Clark S, et al. Prospective multicenter study of the viral etiology of bronchiolitis in the emergency department. Acad Emerg Med 2008;15:111-8.
14. Meissner HC. Selected populations at increased risk from respiratory syncytial virus infection. Pediatr Infect Dis J 2003;22:S40-45.
15. Parrott RH, Kim HW, Arrobio JO, et al. Epidemiology of respiratory syncytial virus infection in Washington, DC II. Infection and disease with respect to age, immunologic status, race and sex. Am J Epidemiol 1973;98:289-300.

16. Shay DK, Holman RC, Roosevelt GE, et al. Bronchiolitis-associated mortality and estimates of respiratory syncytial virus-associated deaths among US children, 1979-1997. J Infect Dis 2001;183:16-22.
17. Miller EK, Gebretsadik T, Carroll KN, et al. Viral etiologies of infant bronchiolitis, croup and upper respiratory illness during 4 consecutive years. Pediatr Infect Dis J 2013;32:950-5.
18. Mansbach JM, Piedra PA, Teach SJ, et al. Prospective multicenter study of viral etiology and hospital length of stay in children with severe bronchiolitis. Arch Pediatr Adolesc Med 2012;166:700-6.
19. Hasegawa K, Pate BM, Mansbach JM, et al. Risk factors for requiring intensive care among children admitted to ward with bronchiolitis. Acad Pediatr 2015;15:77-81.
20. Corneli HM, Zorc JJ, Holubkov R, et al. Bronchiolitis: clinical characteristics associated with hospitalization and length of stay. Pediatr Emerg Care 2012;28:99-103.
21. Damore D, Mansbach JM, Clark S, et al. Prospective multicenter bronchiolitis study: predicting intensive care unit admissions. Acad Emerg Med 2008;15:887-94.
22. Wang EE, Law BJ, Boucher FD, et al. Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) prospective study of risk factors and outcomes in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. J Pediatr 1995;126:212-9.
23. Bekhof J, Reimink R, Brand PL, et al. Systematic review: insufficient validation of clinical scores for the assessment of acute dyspnoea in wheezing children. Paediatr Respir Rev 2014;15:98-112.
24. Schuh S, Lalani A, Allen U, et al. Evaluation of the utility of radiography in acute bronchiolitis. J Pediatr 2007;150:429-33.
25. Hall CB, Powell KR, Schnabel KC, et al. Risk of secondary bacterial infection in infants hospitalized with respiratory syncytial viral infection. J Pediatr 1988;113:266-71.
26. Thorburn K, Harigopal S, Reddy V, et al. High incidence of pulmonary bacterial co-infection in children with severe respiratory syncytial virus (RSV) bronchiolitis. Thorax 2006;61:611-5.
27. Ralston S, Hill V, Waters A, et al. Occult serious bacterial infection in infants younger than 60 to 90 days with bronchiolitis: a systematic review. Arch Pediatr Adolesc Med 2011;165:951-6.
28. Levine DA, Platt SL, Dayan PS, et al. Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections. Pediatrics 2004;113:1728-34.
29. McCallum GB, Plumb EJ, Morris PS, et al. Antibiotics for persistent cough or wheeze following acute bronchiolitis in children. Cochrane Database Syst Rev 2012;CD009834 1-4; 11-15.
30. Oakley E, Borland M, Neutze J, et al. Nasogastric hydration versus intravenous hydration for infants with bronchiolitis: a randomised trial. Lancet Respir Med 2013;1:113-20.
31. Mussman GM, Parker MW, Statile A, et al. Suctioning and length of stay in infants hospitalized with bronchiolitis. JAMA Pediatr 2013;167:414-21.
32. Ross PA, Newth CJ, Khemani RG, et al. Accuracy of pulse oximetry in children. Pediatrics 2014;133:22-9.
33. Unger S, Cunningham S. Effect of oxygen supplementation on length of stay for infants hospitalized with acute viral bronchiolitis. Pediatrics 2008;121:470-5.
34. Hunt CE, Corwin MJ, Lister G, et al. Longitudinal assessment of hemoglobin oxygen saturation in healthy infants during the first 6 months of age. Collaborative Home Infant Monitoring Evaluation (CHIME) study group. J Pediatr 1999;135:580-6.
35. Rietveld S, Colland VT. The impact of severe asthma on school children. J Asthma 1999;36:409-17.
36. Roja-Reyes MX, Granados Rugeles C, Charry-Anzola LP, et al. Oxygen therapy for lower respiratory tract infections in children between 3 months and 15 years of age. Cochrane Database Syst Rev 2009;CD005975 1-7; 13-28.
37. Milesi C, Essouri S, Pouyau R, et al. High flow nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) for the initial respiratory management of acute viral bronchiolitis in young infants: a multicenter randomized controlled trial (TRAMONTANE study). Intensive Care Med 2017;43:209-16.
38. Wing R, James C, Maranda LS, et al. Use of high-flow nasal cannula support in the emergency department reduces the need for intubation in pediatric acute respiratory insufficiency. Pediatr Emerg Care 2012;28:1117-23.
39. Weiler T, Kamerkar A, Hotz J, et al. The relationship between high flow nasal cannula flow rate and effort of breathing in children. J Pediatr 2017;189:66-71.
40. Frizzola M, Miller TL, Rodriquez ME, et al. High-flow nasal cannula: impact on oxygenation and ventilation in an acute lung injury model. Pediatr Pulmonol 2011;46:67-74.
41. Kallappa C, Hufton M, Millen G, et al. Use of high flow nasal cannula oxygen (HFNCO) in infants with bronchiolitis on a paediatric ward: a 3-year experience. Arch Dis Child 2014;99:790-1.
42. Kepreotes E, Whitehead B, Attia J, et al. High-flow warm humidified oxygen versus standard low-flow nasal cannula oxygen for moderate bronchiolitis (HFWHO RCT): an open, phase 4, randomised controlled trial. Lancet 2017;389:930-9.
43. Abboud PA, Roth PJ, Skiles CL, et al. Predictors of failure in infants with viral bronchiolitis treated with high-flow, high-humidity nasal cannula therapy. Pediatr Crit Care Med 2012;13:343-9.
44. Hartling L, Fernandes RM, Bialy L, et al. Steroids and bronchodilators for acute bronchiolitis in the first two years of life: systematic review and meta-analysis. BMJ 2011;342:d1714.
45. Hartling L, Wiebe N, Russell K, et al. A meta-analysis of randomized controlled trials evaluating the efficacy of epinephrine for the treatment of acute viral bronchiolitis. Arch Pediatr Adolesc Med 2003;157:957-64.
46. Plint AC, Johnson DW, Patel H, et al. Epinephrine and dexamethasone in children with bronchiolitis. N Engl J Med 2009;360:2079-89.
47. Chavasse R, Seddon P, Bara A, et al. Short acting beta agonists for recurrent wheeze in children under 2 years of age. Cochrane Database Syst Rev 2002;CD002873 1-2; 3-8.
48. Macias CG, Mansbach JM, Fisher ES, et al. Variability in inpatient management of children hospitalized with bronchiolitis. Acad Pediatr 2015;15:69-76.
49. Bryan MA, Desai AR, Wilson L, et al. Association of bronchiolitis clinical pathway adherence with length of stay and costs. Pediatrics 2017;139e20163432, https://doi.org/10.1542/peds.2016-3432.
50. Shein SL, Rotta AT, Speicher R, et al. Corticosteroid therapy during acute bronchiolitis in patients who later develop asthma. Hosp Pediatr 2017;7:403-9.
51. Mandelberg A, Amirav I. Hypertonic saline or high volume normal saline for viral bronchiolitis: mechanisms and rationale. Pediatr Pulmonol 2010;45:36-40.
52. Zhang L, Mendoza-Sassi RA, Wainwright C, et al. Nebulized hypertonic saline solution for acute bronchiolitis in infants. Cochrane Database Syst Rev 2008;CD006458 1-7; 12-20.
53. Wu S, Baker C, Lang ME, et al. Nebulized hypertonic saline for bronchiolitis: a randomized clinical trial. JAMA Pediatr 2014;168:657-63.
54. American Academy of Pediatrics Committee on Infectious Diseases, Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics 2014;134:415-20.