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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

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.\textsuperscript{13} By age 2 years 90% of children have been infected with RSV, and 40% will contract a lower respiratory tract infection.\textsuperscript{14,15} Reinfection with RSV is common since a primary infection does not confer any immunity.\textsuperscript{16} Rhinovirus is the second most common viral pathogen causing bronchiolitis and is associated with recurrent wheezing.\textsuperscript{15} Other less common etiologies include influenza, human metapneumovirus, coronavirus, parainfluenza, adenovirus, and human bocavirus.\textsuperscript{13,17} One third of children hospitalized with bronchiolitis will have co-infection with two or more viruses.\textsuperscript{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.\textsuperscript{14,19}

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**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.\textsuperscript{7}

Persistent increased respiratory effort, severe tachypnea, hypoxemia, apnea, or intolerance of feeds may warrant hospitalization.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

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**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.\textsuperscript{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.\textsuperscript{7,24} In a nine year prospective study of 565 children hospitalized with RSV only 0.9 percent developed subsequent bacterial pneumonia.\textsuperscript{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.\textsuperscript{26}

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**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.\textsuperscript{19} 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.\textsuperscript{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%.\textsuperscript{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.\textsuperscript{9} 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%. 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.

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.

**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 (SpO2) accuracy in reflecting arterial partial pressure of oxygen (SaO2) is poor below 90% but accurate within 1% of SaO2 when reading above 90%.32 Based on the oxyhemoglobin dissociation curve, when SpO2 is less than 90% incremental increases in SaO2 are associated with significant improvement in SpO2. But when SpO2 is greater than 90% any further increases requires much larger elevations in SaO2.

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

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**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       | Nebulized epinephrine            |
| hydration & nutrition            |                                  |
| Supplemental oxygen              | Hypertonic saline                |
| Respiratory support              | Corticosteroids                  |
| (HFNC, CPAP/BiPAP, MV)           |                                  |
Carbon dioxide concentrations in the blood have a greater impact on the respiratory drive than oxygen saturations. 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. Consider discharge home with close follow up, for children with SpO₂ 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. Avoiding the possible adverse effects of intubation (laryngeal nerve injury, sub-glottic 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 FiO₂ and positive end expiratory pressure (2.5 cm H₂O with flow 6 L). 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.

HFNC also improves gas exchange by washing out CO₂ from pulmonary dead space and decreasing rates of intubation and mechanical ventilation. 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. 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. 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 pCO₂.

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, 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.

**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. (Figure 1)

Consistent clinical benefit has not been shown with the use of β - 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. 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.

**Albuterol**

A Cochrane systematic review of albuterol use in bronchiolitis demonstrated potential adverse effects and increased cost of care without any clear clinical benefit. 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. 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. 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, 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.

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. A trial of albuterol or nebulized epinephrine as a rescue agent in severe disease may be warranted. 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. 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%. 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. 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. 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. Adherence to standardized clinical practice pathways and guidelines is associated with reduced LOS and healthcare costs.

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. 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. Even in young children with virus-associated wheezing, randomized controlled trials have not shown oral steroids to be beneficial. 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% FiO2 for at least 28 days after birth |
| Infants 12-24 months with CLD still requiring O2, 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.  

Hypertonic Saline

Theoretically hypertonic saline increases mucociliary clearance and rehydrates the airway surface liquid. 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. Subsequent well-designed randomized trials reiterate the lack of effect on hospitalization rates but fail to show any improvement in hospital LOS. 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 acentic lesions), and those with chronic lung disease. (Table 2) Prophylaxis consists of a maximum of 5 monthly doses (15 mg/kg/dose) from the start of RSV season.

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.

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.

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