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Bronchiolitis: An Evidence-Based Approach to Management

Jeffrey A. Seiden, MD,*† Richard J. Scarfone, MD*†

Bronchiolitis is a common respiratory illness in infancy for which there is a great deal of clinical practice variation, leading to costly resource utilization without clear evidence for benefit. Recent literature has focused on developing a broad base of evidence through systematic reviews and meta-analyses. This review will focus on this literature as it relates to pharmacologic and nonpharmacologic therapies and other management decisions. In addition, it will highlight some emerging evidence regarding the management of bronchiolitis and innovative new therapies.

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Bronchiolitis was first described as a distinct clinical entity in 1941 after a small influenza epidemic affected a large number of young children in the United Kingdom. Hubble and Osborn [1] wrote that "acute bronchiolitis is the essential pulmonary lesion in epidemic influenza… This condition is particularly common in young children, in whom it produces urgent dyspnoea and, if not vigorously treated, death by asphyxia." Since that time, many more viruses have been implicated in bronchiolitis, including respiratory syncytial virus (RSV) and human metapneumovirus. It has become one of the most common diagnoses made by pediatric emergency physicians.

Despite the frequency with which bronchiolitis is diagnosed, there exists a great deal of variation in clinical practice. Plint et al [2] examined the management of bronchiolitis in 7 different Canadian pediatric emergency departments (EDs). Viral testing was performed on 31% to 92% of patients, and this varied depending on site ($P < .0001$). Half of these patients were discharged home, indicating that inpatient cohorting was not the only indication for testing. Similarly, treatment with a bronchodilator differed among sites, with 59% to 100% of patients receiving at least one such treatment. Some sites used only salbutamol (albuterol), some used only epinephrine, and some used a combination of the two. Such lack of consensus has been reported among inpatients with bronchiolitis as well. In a study of 36 international pediatric centers, Behrendt et al [3] demonstrated that the management of RSV bronchiolitis was strongly influenced by where the child was hospitalized, even when adjusted for patient symptoms and risk factors. Importantly, although differences in care do not seem to influence the course of disease, these variations do account for significantly longer hospital length of stay and higher hospital costs [4].

Over the previous few decades, the number of hospitalizations for bronchiolitis has risen at an alarming rate. The annual bronchiolitis hospitalization rate for children younger than 1 year increased by 240%, from 12.9 per 1000 in 1980 to 31.2 per 1000 in 1996, whereas rates for other lower respiratory diseases have remained stable [5]. Reasons for this increase are unclear. Interestingly, there is some preliminary evidence that the increasing incidence of vitamin D deficiency in children may be contributing to more severe disease [6-10]. This may relate to the role of

*Department of Pediatrics, The University of Pennsylvania School of Medicine, Philadelphia, PA.
†Department of Emergency Medicine, The Children's Hospital of Philadelphia, Philadelphia, PA.
Reprint requests and correspondence: Jeffrey A. Seiden, MD, Department of Emergency Medicine, The Children's Hospital of Philadelphia, 34th St. and Civic Center Blvd, Philadelphia, PA 19104.
(E-mails: seidenj@email.chop.edu, scarfone@email.chop.edu)

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vitamin D in the proper functioning of the innate immune system. Research in this area is ongoing and may lead to population-based interventions that can alter the epidemiology of bronchiolitis.

Also contributing to the trend of increasing hospitalizations is the current disparity among physicians and institutions in the management of bronchiolitis and the lack of a universally accepted clinical score for assessing disease severity. Certainly, such practice variation adds to the difficulty in systematically evaluating potential treatment options. As a result, some institutions have implemented clinical practice guidelines to standardize an approach to bronchiolitis. Most of these guidelines have been applied to the inpatient setting, and it is clear that they are capable of influencing resource utilization without negatively impacting clinical outcomes [11-13]. In 2006, the American Academy of Pediatrics (AAP) [14] published a clinical practice guideline for the diagnosis and management of bronchiolitis, which encompassed a broad range of topics and patient care settings. In light of this, it is essential that we critically examine the evidence that impacts the care of patients with acute bronchiolitis in an effort to develop similar clinical practice guidelines for use in the ED. This review will focus on the most recent developments in the literature related to bronchiolitis, especially highlighting emerging evidence for novel and innovative therapeutic interventions.

Diagnostic Testing

Bronchiolitis is generally diagnosed on the basis of typical history and physical examination findings. Patients are usually younger than 2 years, presenting with cough, coryza, and first-time wheezing. This is preceded by a few days of upper respiratory symptoms, such as rhinorrhea and nasal congestion. Despite this easily recognizable clinical presentation, many clinicians use chest radiography as an adjunct in the diagnosis of bronchiolitis. In a study of 30 large children's hospitals, chest radiographs were obtained in 72% (range, 38%-89%) of patients admitted with bronchiolitis [15]. Radiographic results may be helpful in differentiating bronchiolitis from other disease entities, such as foreign body aspiration, congestive heart failure, or a mediastinal mass. However, in a recent cohort of 265 nontoxic appearing infants with typical bronchiolitis, as defined above, chest radiography results were inconsistent with the clinical diagnosis in only 2 (0.75%) patients [16]. The acute management for both patients was unaffected by these results. On the other hand, obtaining chest radiographs increased the number of patients who were prescribed antibiotics. Although the treating physicians were planning to give antibiotics to only 2.6% of patients before obtaining the test, this number increased to 15% after the physicians viewed the images. It is likely that antibiotic treatment was unnecessary for most of these patients. Considering this evidence, the routine use of chest radiography is not warranted and should be reserved for atypical cases in which other diagnoses are being considered.

Viral testing is another commonly used adjunct in patients diagnosed with bronchiolitis. Among 30 children's hospitals, RSV testing was performed for 60% (range, 26%-92%) of infants admitted for bronchiolitis [15]. However, a systematic review of the literature has suggested that results of such testing rarely alters patient management [17]. Moreover, the utility of viral testing varies with the community prevalence of disease; the predictive value of the tests are greatest during high-prevalence seasons, when the clinical diagnosis is most evident. Some advocate RSV testing to assist with inpatient cohorting decisions; this has been shown to reduce nosocomial infections and be cost-effective [18] However, cohorting patients based on symptoms rather than test results may help to decrease the spread of RSV and other viruses associated with bronchiolitis [11]. In light of this, routine viral testing is likely not cost-effective or helpful in the acute management of bronchiolitis.

It has also been suggested that viral testing can be helpful in the evaluation of the young infant with bronchiolitis and fever, in whom serious bacterial infections are being considered. In fact, a large multicenter study of 1248 febrile neonates (<2 months of age) found that serious bacterial infections were significantly less common in RSV-positive patients (7.0%) than in RSV-negative patients (12.5%) [19]. Most of the bacterial infections in the RSV-positive group were urinary tract infections (5.4%), and there were no cases of bacterial meningitis. However, among the subset of neonates younger than 1 month, there were no differences in the rates of serious bacterial infection between the 2 groups. Importantly, because shedding of RSV can persist for weeks, a positive test from a prior infection can certainly accompany a subsequent bacterial infection. As a result, it is probably more important to determine the prevalence of concurrent bacterial infections among neonates with the clinical signs and symptoms of bronchiolitis. In the same study of febrile neonates, those with clinical bronchiolitis had a similarly low prevalence of bacterial infections (7.1%; no cases of bacteremia or bacterial meningitis). Thus, clinical assessment is likely sufficient to replace viral testing in determining the need for further diagnostic evaluation.

For nonneonates with bronchiolitis, multiple studies have demonstrated very low rates for concurrent serious bacterial infections [20,21]. Ultimately, the extent of the diagnostic workup for fever in a patient with bronchiolitis depends on multiple factors. For an infant younger than 1 month, a full evaluation for sepsis is indicated. In an infant 1 to 2 months old, routine screening for urinary tract infection is certainly warranted; screening for bacteremia and meningitis may be based on clinical factors and the patient's general appearance. For an older

infant or toddler, one should consider other risk factors and perform selective screening, especially for urinary tract infection, accordingly.

Therapy

As with diagnostic testing, there is a high degree of practice variability with respect to therapeutic measures for bronchiolitis. Many therapies that have proven effective in other disease entities, such as asthma and cystic fibrosis, have been used, although it is important to recognize differences in pathophysiology that may lead to different clinical responses. Recent literature has focused on systematically analyzing the available data regarding common therapies to determine whether it supports their routine use. Overall, it seems that supportive care should be the cornerstone of management and that most pharmacologic measures offer limited, if any, benefit in the treatment of bronchiolitis.

Short-acting β_2-agonists (SABAs) are widely considered among the first-line agents for bronchiolitis, and they have been studied extensively. Although the results of individual studies vary, pooled analysis of these studies (Figure 1) demonstrates a small but statistically significant improvement in clinical score in response to SABA therapy [22]. Because of the heterogeneity in these studies, though, it is difficult to determine the clinical importance of this short-term benefit. Moreover, adverse effects, such as tachycardia and agitation, are substantially more common in those patients receiving SABA. Examining the data more closely reveals that a large proportion of infants (43%) in the control groups for these studies demonstrated a clinical improvement as well. These improvements could be related to the minute-to-minute variability that is typical of the disease process or to fever reduction with a concomitant decrease in respiratory rate. This is compared to the 57% of patients treated with SABA who demonstrated some clinical improvement. If this absolute rate of

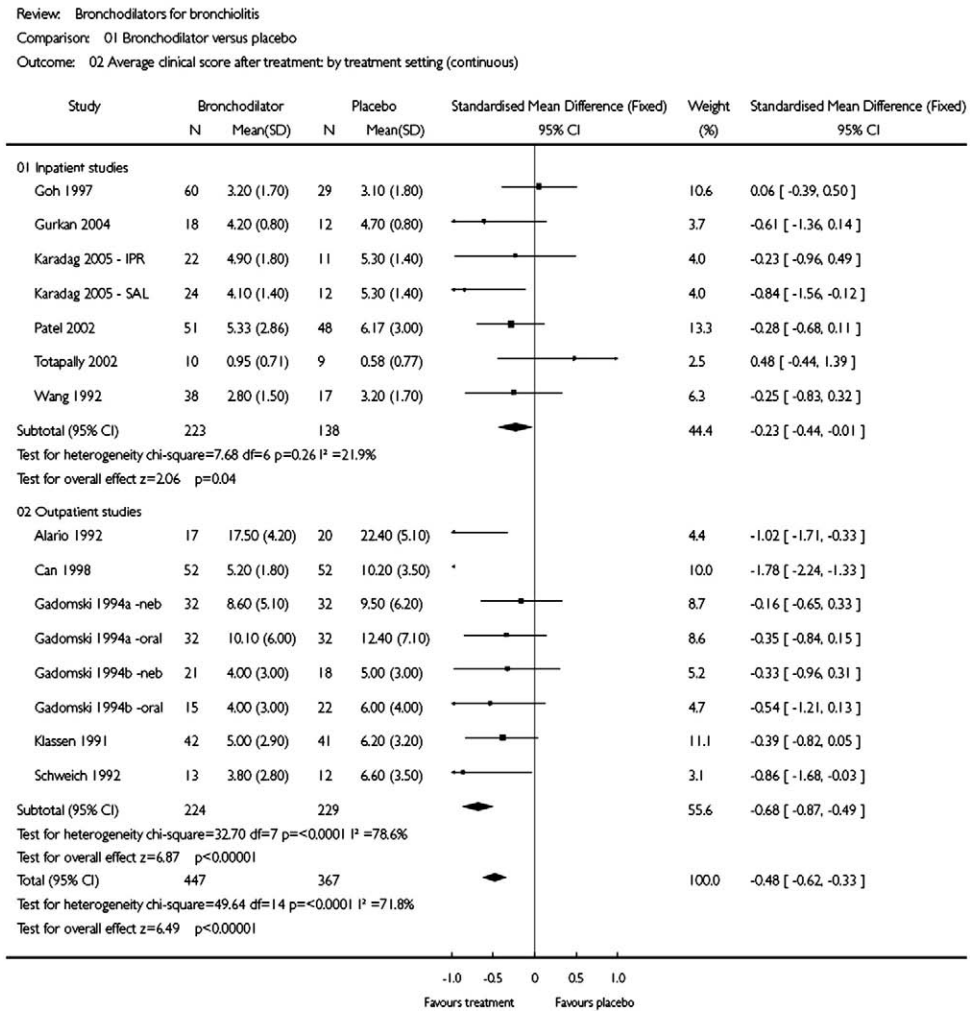

Figure 1 Cochrane Collaboration systematic review of studies assessing difference in rate of improvement after beta2-agonist bronchodilators or placebo among children with bronchiolitis (from Gadomski AM, Bhasale AL. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev 2006;3:CD001266. Copyright Cochrane Collaboration, used with permission).

improvement difference (14%) is assumed to be true, that would represent a short-term improvement attributable to the SABA therapy in approximately 1 of 7 patients treated. An additional 3 of 7 would demonstrate improvement as well, but it would be unrelated to the SABA therapy. Consequently, the small potential benefit of routine SABA treatment must be weighed against the potential negative effects associated with these agents. Furthermore, studies have nearly universally found no effect of SABA on the rate of hospitalization or other longer term outcomes [22]. Although SABAs remain a therapeutic option, it is essential that they are continued only in patients for whom a clinical improvement after treatment has been documented.

Nebulized epinephrine, which has both β_2-agonist and α-agonist activity, has also been proposed as a useful therapy in bronchiolitis. A recent Cochrane Collaboration systematic review compared nebulized epinephrine with placebo and with SABA with respect to several clinical outcomes [23]. Overall, epinephrine compares favorably with placebo in its short-term effect on clinical score. However, it does not seem to reduce the need for hospitalization among outpatients. The adverse effects are similar to those of SABA, and in most institutions, epinephrine is not considered an outpatient treatment option. In general, nebulized epinephrine should be considered for those patients who have moderate to severe distress, will require hospitalization, and in whom SABA therapy was ineffective. Again, treatment should be continued only in those patients for whom a clinical improvement is observed.

Systemic corticosteroids remain a commonly prescribed therapy for bronchiolitis, likely related to their known effectiveness in the treatment of asthma. Because of the paucity of evidence for their benefit, though, it seems that many ED clinicians are abandoning the routine use of corticosteroids. While corticosteroids were administered to one-quarter of patients hospitalized with bronchiolitis in earlier studies [3,4], a more recent study that focused on ED management of bronchiolitis found that fewer than 4% of patients were treated with systemic corticosteroids [2]. The Pediatric Emergency Care Applied Research Network, consisting of 20 US EDs, conducted a multicenter, randomized, controlled trial of dexamethasone for the treatment of bronchiolitis among 600 previously healthy patients between 2 and 12 months of age. This landmark study found no difference in hospital admission rates, clinical severity scores, length of stay for admitted patients, or adverse events for those treated with corticosteroids [24]. In addition, the Pediatric Emergency Care Applied Research Network study analyzed potential subgroups that might differentially benefit from steroid treatment, including those with a personal or family history of atopy or asthma; dexamethasone treatment did not yield any benefit for these children either.

Another large, multicenter study was recently presented by the Pediatric Emergency Research Canada group in abstract form. This study also found no difference in hospitalization rates for those treated with dexamethasone alone when compared with placebo [25]. Interestingly, they did find a reduction ranging from 26% to 18% in hospitalization rate for patients treated with the combination of dexamethasone and nebulized epinephrine, despite finding no benefit for either agent individually. The magnitude of the benefit on an individual patient level was modest, with 11 patients needing to be treated to prevent 1 hospitalization compared with placebo controls. However, when extended across the large population of children with bronchiolitis, the relative benefit of a reduction in hospitalization rate by 31% would be substantial. The scientific interpretation and practical translation of these findings to the clinical environment will be an area of interest as these results are published formally.

Anticholinergic agents, such as ipratropium bromide, have been studied in multiple small ED-based trials. A recent meta-analysis demonstrated that these medications provided no benefit when used alone or as an adjunct to SABA therapy [26]. Similarly, while early observation studies seemed to indicate that inhaled corticosteroids given in the acute phase of bronchiolitis might prevent future wheezing, the Cochrane group demonstrated that inhaled corticosteroids did not prevent postbronchiolitic wheezing, nor did they reduce the rate of rehospitalization after discharge from the ED [27].

Chest physiotherapy is used in many respiratory diseases as a way to assist in clearing tracheobronchial secretions in an effort to relieve airway obstruction, reduce airway resistance, enhance gas exchange, and reduce work of breathing. However, in a meta-analysis of 3 randomized controlled trials of chest physiotherapy in acute bronchiolitis, there was no effect on hospital length of stay, supplemental oxygen requirements, or severity as measured by clinical score [28].

Antimicrobial therapy has a very limited role in the management of bronchiolitis. Ribavirin is an RSV-specific antiviral agent, but it is not recommended for routine use in otherwise healthy patients because of its high cost and limited efficacy; it may still be warranted in patients with underlying immunocompromise or in severe cases [14].

Otitis media is the most common bacterial infection associated with bronchiolitis, occurring in up to 50% to 60% of patients [29]. The bacterial pathogens are similar to those recovered in other children with acute otitis media; thus, treatment is according to standard recommendations. Other concurrent bacterial infections are rare in typical cases of bronchiolitis, so antibiotic treatment is not routinely indicated.

Emerging Evidence

There are a variety of other therapies for which the literature continues to evolve. A great deal of literature

supports the use of nebulized hypertonic saline in the treatment of cystic fibrosis, in which clearance of thickened secretions is essential. A recent multicenter trial of 96 patients admitted for bronchiolitis compared nebulized 3% hypertonic saline with nebulized normal saline in a double-blind fashion. The group treated with hypertonic saline had a 26% reduction in hospital length of stay compared with the group treated with nebulized normal saline (2.6 vs 3.5 days, respectively; $P = .05$), and the treatment was well tolerated without any adverse events associated with its use [30]. Other studies seem to support a beneficial adjunctive role for hypertonic saline in the treatment of bronchiolitis as well [31,32].

Macrolide antibiotics are also being investigated for the treatment of bronchiolitis. In addition to their antibacterial effects, macrolides have been demonstrated to have significant immunomodulatory and anti-inflammatory effects. As a result, one group in Turkey conducted a randomized, double-blind, placebo-controlled trial of clarithromycin in the treatment of RSV bronchiolitis [33]. A 3-week course of clarithromycin resulted in significantly decreased hospital length of stay and decreased levels of plasma chemokines, such as IL4 and IL8. In addition, readmission rates within 6 months of discharge were lower in the group receiving clarithromycin. Although there is not nearly enough literature to support the use of macrolide antibiotics in cases of uncomplicated bronchiolitis, this study suggests the need for further investigation.

Approximately 2% to 6% of patients with bronchiolitis require care in an intensive care unit, and more than half of these patients ultimately require mechanical ventilation. For these severely affected infants, there are some less invasive treatments that may prevent the need for endotracheal intubation. A mixture of helium and oxygen, or heliox, is a treatment that is posited to improve laminar flow through airways with increased resistance. In a prospective, randomized, double-blind study of infants younger than 3 months admitted with RSV bronchiolitis to the intensive care unit, one study group found a rapid and significant improvement in overall respiratory status in the group treated with heliox compared with the group treated with the standard air-oxygen mixture [34]. Interestingly, though, when the Canadian Critical Care Trials group designed a multicenter, randomized, double-blinded trial of helium-oxygen vs air-oxygen, they found that both groups had similar rates of endotracheal intubation, approximately 20% in each group [35]. Although it seems that heliox can provide some short-term benefit with respect to work of breathing and wheezing, larger studies are needed to elucidate its ability to decrease the need for mechanical ventilation in patients with severe bronchiolitis.

Continuous positive airway pressure (CPAP) has also been studied in patients with severe or refractory disease. In a randomized, controlled, crossover study of 31 patients with moderately severe bronchiolitis, nasal CPAP was well tolerated and improved carbon dioxide elimination when compared with standard treatment [36]. A small study of 12 patients with severe refractory bronchiolitis confirmed that CPAP improves clinical score and carbon dioxide clearance. In addition, using heliox seemed to augment these benefits [37]. Larger studies are necessary to determine whether CPAP alone, or in combination with heliox, can affect the rate of endotracheal intubation.

Disposition and Predicting Outcomes

An essential component in the evaluation and management of bronchiolitis in the ED is the ability to predict its natural course and assess the risk of progression to more severe disease. Infants' symptoms generally worsen for the first 3 to 5 days and then gradually improve, sometimes over a prolonged period. According to one series, nearly 40% of patients remain symptomatic at 2 weeks and nearly 1 in 10 will not have returned to baseline even at 4 weeks [38]. It is important to explain this when providing anticipatory guidance to families. Because it is a dynamic disease, evaluations at a single point in time may not be sufficient to fully estimate its severity. Minute-to-minute variability necessitates serial examinations during an ED visit.

Many studies have attempted to identify history and physical examination factors that predict progression of disease. Collecting data from 30 US EDs, Mansbach et al [39] conducted a large, prospective, multicenter cohort study to determine which patients are safe to discharge from the ED. The historical factors found to be significantly associated with safe discharge included older age ($\geq$2 months) and no prior endotracheal intubations. In another study of 213 patients followed after an ED visit for bronchiolitis, Shaw et al [40] also found that young age (defined as <3 months) is a risk factor for severe disease, defined by not remaining alert, active, and able to maintain hydration with oral fluids throughout the disease course. In addition, prematurity (gestational age <34 weeks) was associated with an increased likelihood of developing severe disease (Relative Risk (RR), 2.6). Other findings that have consistently been associated with severe disease include congenital heart disease, chronic lung disease, and underlying immunodeficiency [41].

Apnea is one of the most concerning complications of bronchiolitis in young infants, although it seems to be rare and limited to a specific high-risk population defined by certain historical factors. In a recent retrospective cohort of 691 patients treated and admitted for bronchiolitis from an urban, tertiary care pediatric ED, 19 (2.7%) subsequently developed apnea during their hospital admission [42]. All of these patients were identified by having 1 or

more of the following risk factors: (1) a history of an apneic episode having already occurred, (2) age less than 1 month in full-term infants, or (3) postconceptual age less than 48 weeks in premature infants. Of the 429 patients without any of these risk factors, none experienced apnea during admission.

Physical examination findings at the time of presentation have not been as consistently associated with outcomes, likely secondary to the high degree of short-term variability in bronchiolitis. Not surprisingly, severe tachypnea and toxic appearance have been associated with more severe disease [39,40]. Hypoxemia (oxygen saturation as measured by pulse oximetry, <94%-95%) is also identified as a predictor of disease progression in these studies. However, it is unclear what the significance of mild hypoxemia (oxygen saturation as measured by pulse oximetry, 90%-95% at sea level) is with respect to short- and long-term outcomes for otherwise healthy infants. The routine use of pulse oximetry has allowed clinicians to detect subclinical hypoxemia. Bronchiolitis generally causes hypoxemia because of subsegmental atelectasis and mucus plugging, which lead to transient ventilation-perfusion mismatch.

The institution of supplemental oxygen therapy is another area of controversy and wide practice variation. In a survey of the Pediatric Emergency Medicine section of the AAP, the authors presented multiple clinical vignettes that varied individual factors, including oxygen saturation, while keeping other parameters constant. They found that simply changing the hypothetical patient's oxygen saturation from 94% to 92% resulted in dramatic changes in management decisions. The likelihood of giving supplemental oxygen more than doubled from 39% to 81% and the rate of hospital admission increased from 58% to 85% based on this variable alone [43]. However, there is not sufficient evidence to support the use of supplemental oxygen for mild hypoxemia. Furthermore, there is a great deal of literature that suggests that arbitrary thresholds for supplemental oxygen therapy may be increasing medical costs without any clear benefit [44-46]. In response to this conflicting and controversial evidence, the AAP practice guideline advises that supplemental oxygen should be used in patients for whom the oxygen saturation falls persistently below 90% despite simple maneuvers such as nasal suctioning and repositioning. Furthermore, when an infant is improving clinically, the use of continuous pulse oximetry can be replaced with intermittent spot checks [14].

Ultimately, the decision regarding patient disposition from the ED involves a variety of factors. Assessing the patient's risk for a more severe clinical course is paramount and includes understanding the natural course of the disease process. Moreover, gauging the infant's ability to maintain hydration with oral fluids and the family's ability to follow up with their primary provider and understand the signs of worsening disease are essential.

Summary

Bronchiolitis is a common respiratory disease in infancy, and it results in a large number of health care visits and expenditures. Despite an abundance of literature addressing various treatment modalities, management remains largely supportive. Emergency department clinicians must continue to develop a comprehensive understanding of the dynamic and variable nature of the disease process and be able to effectively predict the severity of its clinical course. Finally, there is emerging evidence that highlights some newer therapies, such as nebulized hypertonic saline, that may change the way in which bronchiolitis is treated in the ED; vigilance in monitoring the literature is essential to ensure that patients are treated in the most efficient and effective manner.

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