Update on management of bronchiolitis
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\textbf{Purpose of review}
Bronchiolitis impacts millions of infants worldwide. Although several therapeutic options stem from highly plausible theoretical rationales for success and some may even offer modest short-term symptom relief, none has been conclusively shown to alter the course of the disease or its major outcomes. However, several recent papers shed light on which treatments show promising preliminary evidence and offer insight into future research endeavors on this topic. This review will summarize bronchiolitis therapy in view of this recent evidence.

\textbf{Recent findings}
The agents in which theory promises but treatment does not deliver include systemic corticosteroids alone, inhaled bronchodilators alone and antileukotrienes. The most promising combination to date appears to be that of oral dexamethasone and inhaled epinephrine but numerous related issues need to be clarified further. Caretakers need to be counselled about the usual protracted clinical course of bronchiolitis.

\textbf{Summary}
Because bronchiolitis is a highly heterogeneous entity, future research challenges should include detailed characterization of infants most likely to benefit from given interventions. In the meantime, stick with the good old time-honored supportive route!

\textbf{Keywords}
bronchiolitis, dexamethasone, epinephrine, heliox, respiratory distress

\textit{Curr Opin Pediatr} 23:110–114
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1040-8703

\textbf{Introduction}
Bronchiolitis is the leading cause of infant hospitalizations during the first year of life [1]. It is usually defined as the first viral episode of respiratory distress, accompanied by coryza, cough, crepitations and wheezing [2]. The respiratory syncytial virus (RSV) accounts for the majority of cases [3], although other important viruses have also been implicated [4–6]. Several excellent reviews of the etiology and treatment approaches to bronchiolitis have recently been published [7–11], all of which highlight importance of oxygenation, hydration and airway support if necessary [12,13].

However, no single pharmacological agent has been conclusively found to change the course of the disease. An important challenge is that bronchiolitis has wide etiologic heterogeneity, encompassing the only episode of viral-induced wheezing and the first attack of episodic wheezing without atopy/interval symptoms as well as the initial exacerbation of a multitrigger wheeze often associated with asthma [7]. The bad news is that these wheezing phenotypes respond differently to treatment [7]. Because it is impossible to reliably identify these subgroups during their initial presentation, interpretation of the results of therapeutic trials of bronchiolitis becomes challenging [14,15].

In 2006, the American Academy of Pediatrics (AAP) released a comprehensive evidence-based guideline on the management of bronchiolitis [16]. Since then, two large multicenter bronchiolitis trials have shed light on the management with oral dexamethasone with and without nebulized epinephrine [17**,18] and raised several unanswered questions. Furthermore, several recent systematic reviews of various other inhaled therapies guide us when these interventions may be effective [19–21]. Two recent bronchiolitis papers have clarified predictors of the return for care after discharge from the emergency department (ED) [22*] and highlighted the usual protracted course of this disease [9]. This review will therefore focus on the update of pharmacotherapy in bronchiolitis in light of this recent information.

\textbf{Supplemental oxygen}
Since the invention of routine transcutaneous oxygen saturation monitoring two decades ago, the hospitalization rate for bronchiolitis has increased 2.5-fold, without increase in mortality [23]. Several authors postulate the...
use of oximetry is at least in part related to this increase in admissions [24]. The significance of mild hypoxemia with saturations below 95% as it relates to bronchiolitis outcomes has not been specifically studied and the thresholds for administering supplemental oxygen vary widely [25–29]. Indeed, a small difference in oximetry of minimal physiologic significance between 94 and 92% has been shown on its own to raise postulated hospitalization rate from 58 to 85% [24]. Another study showed that approximately 26% of infants with bronchiolitis experience prolonged hospital stays based on periodic desaturations, despite satisfactory clinical status [30,31]. As a result of the arbitrary nature of various thresholds for using supplemental oxygen which are likely not cost-effective [31–33], the AAP recommends the use of this intervention in previously healthy infants with saturations below 90% [16]. Further studies of the impact of desaturations and mild hypoxemia on bronchiolitis outcomes are needed.

**Bronchodilators**

Both nebulized epinephrine and albuterol are commonly given for bronchiolitis, with highly variable frequency [34]. The attractive features of inhaled epinephrine in bronchiolitis include its vasoconstrictive and beta agonist properties [35,36]. Because patients with bronchiolitis are a highly heterogeneous group, some of whom may have their first asthma episode, the AAP guideline recommends that a monitored trial of a bronchodilator may be given [16]. However, this guideline strongly advises against routine use of bronchodilators in this disease and recent evidence outlined below certainly points to this conclusion.

Of the four studies published since 2003 focusing on short-term outcomes after nebulized epinephrine versus albuterol/placebo in bronchiolitis [37–40], the largest was a multicenter randomized controlled trial from 2008 which found no difference between three consecutive doses of nebulized albuterol and a single dose of epinephrine [40]. Likewise, hospitalized infants given nebulized epinephrine appear to derive no added benefit compared with those treated with albuterol or placebo [33,41]. A systematic review [20] showed four of five inpatient studies demonstrated no benefit of epinephrine over placebo with respect to the clinical score [20]. Although the authors found some evidence of short-term clinical benefit of epinephrine over albuterol in the four included outpatient studies, epinephrine inferred no advantage with respect to hospitalization. They recommend a large randomized controlled trial comparing epinephrine with placebo and salbutamol in the outpatient setting.

A recent Canada-wide trial compared the impact of two doses of nebulized epinephrine, daily oral dexamethasone and the combination of both with the use of two placebos in 800 previously healthy outpatients with bronchiolitis in the ED [17**]. Although infants in the epinephrine group had achieved significantly lower clinical scores during the initial hour of the study compared with those receiving placebo, there was no impact of epinephrine on hospitalization and this intervention was accompanied by more side-effects.

**Corticosteroids**

A recent systematic review of 13 trials of 1198 children with bronchiolitis given systemic corticosteroids showed no difference in hospitalization, length of hospital stay, clinical scores and readmission rates compared with placebo [42]. The AAP guideline also recommends against the use of corticosteroids in bronchiolitis [16].

Since then, two large multicenter placebo-controlled trials have been carried out [17**,18]. The first was a US trial which found that a single high dose of oral dexamethasone conveys no benefit compared with placebo with respect to hospitalizations from the ED, length of stay, return for care or clinical score [18]. Shortly thereafter, the aforementioned Canada-wide study by Plint et al. [17**] used a factorial design to compare the effect of daily dexamethasone alone, two doses of inhaled epinephrine in the ED alone and the combination of the two with using two placebos. Although neither agent alone produced any benefit, the authors found that the dexamethasone–epinephrine combination resulted in a nine-percentage point reduction in hospitalization within 7 days [17**]. The authors postulated this potential beneficial effect may stem from a synergy between the two therapeutic agents. Although this difference may translate into substantial reduction in hospitalizations in the population as a whole, this effect size is relatively modest. Because the effects of the high dose of dexamethasone used on the brain and lungs of babies are uncertain [43], this treatment cannot be currently recommended without further evidence. For these reasons, it
seems prudent to investigate a corticosteroid dose considerably smaller compared with that used in the study by Plint. The optimal treatment duration is also unknown, and, although a previous small study showed infants given regular albuterol with a single dose of oral dexamethasone achieved outcomes comparable to those given a longer course of corticosteroids, this needs to be verified in a large trial [44].

A recent small but worthwhile study clarifies the reasons for the lack of benefit of isolated steroid therapy in bronchiolitis [45]. The authors showed that dexamethasone fails to produce anti-inflammatory effect in acute RSV bronchiolitis because it lacks sufficient impact on the production of inflammatory cytokines which play a major role in this disease.

**Hypertonic saline**
Both the hypertonic saline and deoxyribonuclease agents work by decreasing viscosity of airway mucus [46–48,49]. A recently published Cochrane Systematic Review of four trials [46,50–52] involving 254 infants with acute bronchiolitis found that 3% saline results in a significantly shorter length of hospital stay as well as a lower clinical score [19]. However, none of these studies involved infants presenting to the ED. A recent small ED study of this population using inhaled hypertonic saline and epinephrine versus normal saline and epinephrine found no difference between these interventions with respect to the improvement in the clinical score, oxygen saturation, hospitalization and return for care [53]. Likewise, two inpatient studies of the deoxyribonuclease have demonstrated no benefit [47,48]. Clearly, not enough compelling evidence currently exists to recommend the use of mucolytic agents in bronchiolitis and further research is necessary.

A recent published review article clarifies the postulated basic science mechanisms of action involving hypertonic saline in bronchiolitis [49]. Hypothetically, hypertonic saline may help reverse some of the pathophysiological abnormalities in bronchiolitis by increasing airway surface thickness, decreasing epithelial edema, improving elasticity and viscosity of mucus as well as accelerating mucus transport rates [49]. Hopefully, the authors’ highly credible rationale for benefit of this agent on the inflamed airway will translate into clinical effect on major outcomes such as hospitalization in a large randomized trial.

**Heliox**
The mixture of helium and oxygen in an 80:20 ratio is much lighter and less dense than air. Because of associated greater laminar and lower turbulent flow, less respiratory effort should be needed for effective breathing [54]. This may be particularly useful in the ICU setting in combination with the continuous positive airway pressure management. However, the evidence to date cannot recommend this intervention for practice. The four studies performed in this setting are all small, one has no control group and two lack blinding [55–58]. Although a recent Cochrane Systematic Review on the subject suggests that the addition of heliox may significantly reduce respiratory distress, heliox appears to show no impact on the rate of intubation or ventilation or the length of ICU stay [21].

**Antibiotics**
Bacteremia rate in febrile infants with bronchiolitis is very low, at 0.2% [59] – much superceded by urinary tract infections and otitis media [60,61]. However, antibiotics should only be used when specific evidence of coexistent bacterial infection is present [16]. Interestingly, the macrolides appear to have anti-inflammatory and immunomodulating properties in addition to their antibacterial activity. However, the clinical evidence of benefit of this class of drugs in bronchiolitis is scarce, with disparate results [62,63]. Infants with severe bronchiolitis requiring assisted ventilation have been found to have surprisingly high bacterial co-infection rate in the tracheal secretions, although to what degree this finding contributes to the clinical manifestation is currently not clear [64]. Although this may be a fruitful area of future research in this highly select population, its results are unlikely to impact the vast majority of infants with bronchiolitis.

**Ribavirin**
Although ribavirin produces good in-vitro activity against the viruses causing bronchiolitis, more recent studies have failed to show its benefit in either the outcomes of infants admitted to the ICU or the rate of viral clearance [65,66]. Because this agent may be teratogenic and is cumbersome to use, the AAP has recently recommended against its routine use [16]. It may be considered for immunosuppressed infants and those with hemodynamically significant cardiac disease.

**Montelukast**
The use of montelukast is another example of where theory promises but treatment does not deliver. Although infants with bronchiolitis have high levels of pro-inflammatory leukotrienes in their airway, a recent randomized controlled trial of oral montelukast in infants under 2 years of age with acute bronchiolitis over 6 months failed to reduce subsequent respiratory symptoms [67].
Continuous positive airway pressure
Infants with progressive hypoxemia and increasing respiratory distress may require continuous positive airway pressure support in the ICU setting which constitutes an effective mode of airway support for early ventilatory decompensation [68,69] and obviates the complications associated with intubation and sedation required for children in frank respiratory failure.

Duration of symptoms and return for care
Recent evidence suggests that many infants seen in the ED for bronchiolitis have a protracted clinical course, with a median disease duration of 15 days, 25% remaining symptomatic after 21 days and 37% experiencing unscheduled medical visits following the ED visit [70]. In 2010 Norwood et al. [22] conducted a study examining predictors of unscheduled medical visits in infants with bronchiolitis discharged home from the ED. They found that the significant independent predictors of this outcome were age less than 2 months, history of prematurity less than 35 weeks of gestation and history of hospitalization [22]. Several years ago, Mansbach et al. [71] also found that the factors associated with a safe discharge home in bronchiolitis include age 2 months and older, without prior endotracheal intubation. The results of these studies are useful in counselling the parents of this population in the ED prior to discharge home.

Immunoprophylaxis
Passive immunization with humanized monoclonal antibody prophylaxis is recommended for infants 2 years of age and younger with hemodynamically significant congenital heart disease requiring pharmacotherapy, those suffering from pulmonary hypotension, infants with chronic lung disease or prematurity who required medical therapy within 6 months of the start of the bronchiolitis season and infants born at or before 32 weeks’ gestation, particularly if they are less than 12 months old during their first bronchiolitis season [16].

Conclusion
The agents unlikely to impact bronchiolitis outcomes include systemic corticosteroids alone, inhaled bronchodilators alone and antileukotrienes. The most promising combination to date appears to be that of oral dexamethasone and inhaled epinephrine, but numerous related issues need to be clarified further. These include, among others, the optimal dose of dexamethasone, duration of treatment and finding out which subset of babies is the most likely to respond. Because bronchiolitis is a highly heterogeneous entity, future research challenges will include detailed characterization of subjects most likely to benefit from given interventions. In the meantime, stick with the good old time-honored supportive route!

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 138–139).

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This is an excellent review of the biologic rationale of the mechanism of action of hypertonic saline in bronchiolitis.


This is the first ED study of hypertonic saline and epinephrine in bronchiolitis.


This article offers invaluable information for counselling caretakers of infants with bronchiolitis in the ED.