Recent evidence on the management of bronchiolitis

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Purpose of review
Bronchiolitis is a common condition in children less than 2 years of age and is a leading cause of infant hospitalization. Although there is significant variability in testing and treatment of children with bronchiolitis, diagnostic testing rarely improves care, and no currently available pharmacologic options have been proven to provide meaningful benefits or improve outcomes.

Recent findings
Beta-agonists continue to be used frequently despite evidence that they do not reduce hospital admissions or length of stay. In general, therapies initially considered promising were subsequently proven ineffective, a pattern seen in studies on corticosteroids, and more recently with nebulized racemic epinephrine and hypertonic saline. Recent research has improved our understanding of the viral epidemiology of bronchiolitis, with increasing recognition of viruses other than respiratory syncytial virus and better awareness of the role of viral coinfections. How these findings will translate into improved outcomes remains uncertain.

Summary
Much of the emphasis of the last few decades of bronchiolitis clinical care and research has centered on the identification and testing of novel therapies. Future quality improvement efforts should focus more on the limitation of unnecessary testing and treatments. Future research should include identification of subgroups of children with bronchiolitis that may benefit from focused clinical interventions.

Keywords
bronchiolitis, hypertonic saline, overutilization, pulse oximetry, respiratory syncytial virus, rhinovirus

INTRODUCTION

Viral bronchiolitis is a leading cause of hospitalization in infants and leads to at least one office visit in approximately 10% of children less than 2 years of age [1]. Despite a lack of supporting evidence, many interventions continue to be used excessively, prompting efforts to curb unnecessary testing and treatments [2▪,3▪]. While there have been some signs of success in reducing excessive care in bronchiolitis [3▪,4–6], substantial overuse and practice variation persist. In this review, we will highlight recent developments in bronchiolitis research, focusing on epidemiology, diagnostic testing, and therapeutics.

EPIDEMIOLOGY

During the 1980s and 1990s, hospitalizations for bronchiolitis increased 2.4-fold in the United States, likely secondary to the advent of widespread pulse oximetry use and the general acceptance of hypoxemia as an admission criterion [7,8]. During the same time, however, bronchiolitis mortality rates did not change [9], suggesting that many of these hospitalizations may have been unnecessary. There are some encouraging signs that the rate of unnecessary hospitalizations is beginning to decrease. From 2000 to 2009, hospitalizations in children 0–11 months of age began to decrease slightly, although the mean charges per hospitalization increased 34%, probably because of an increase in children with high-risk medical conditions and increased severity of disease as demonstrated by increased use of mechanical ventilation [10].

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KEY POINTS

- Although bronchiolitis is a frequent cause of hospitalization and outpatient visits in infants and young children, few interventions are effective other than basic supportive care.
- Many pharmacologic therapies demonstrate initial promise but are proven ineffective in subsequent trials.
- There is increasing recognition of the role of rhinovirus and the frequency and relevance of viral coinfections. While testing for viruses in clinical practice currently has no clear benefit, additional research may clarify whether infants with certain viruses respond more favorably to treatment.

Virology

Recent investigations have better elucidated the viral epidemiology of bronchiolitis and the significance of viral coinfections. In a prospective, multicenter study on bronchiolitis (the Multicenter Airway Research Collaboration 30 (MARC-30) study), involving 2207 children less than 2 years of age, we demonstrated that 30% of children hospitalized with bronchiolitis were infected with more than one virus [11▪▪]. Although most (72%) children in this study were infected with respiratory syncytial virus (RSV), a substantial proportion (26%) were infected with human rhinovirus (HRV). Children with HRV alone were more likely to have a shorter length of stay (LOS), a finding seen previously in a Finnish sample [12]. The MARC study also demonstrated that viral etiology did not predict apnea, challenging a long-held belief that RSV increases the apnea risk more than other viruses in bronchiolitis [13▪]. Finally, the study demonstrated that, while the viral etiology had some impact on LOS, it did not predict the need for positive pressure ventilation (PPV), consistently with another recent investigation [14] suggesting that clinical factors were more predictive of bronchiolitis severity than the viral etiology.

DIAGNOSTIC TESTING

Infants with bronchiolitis often undergo extensive, and largely needless, diagnostic evaluation. The 2006 American Academy of Pediatrics (AAP) bronchiolitis clinical practice guideline (CPG) recommended no routine laboratory or radiologic studies in bronchiolitis [15], but there is evidence that a substantial amount of testing is still performed.

Chest radiographs

Two recent investigations have analyzed trends in emergency department chest x-ray (CXR) use. Knapp *et al.* [16] demonstrated that CXR use did not change between 1995 and 2009, whereas Johnson *et al.* [17] revealed a statistically significant decline from 65%, before the 2006 AAP guidelines, to 49%, after the guidelines. Although this decline is encouraging, CXRs are still being performed on almost half of children with bronchiolitis. CXRs are associated with avoidable costs, radiation exposure, and subsequent antibiotic administration [18]. Because CXRs are generally obtained on presentation, efforts to reduce imaging should focus on emergency medicine and outpatient clinicians. Quality improvement efforts involving pediatric hospitalists do not appear to reduce unnecessary therapies that occur at presentation [3▪].

Viral testing

While the role of virology testing in current clinical care is limited, and is discouraged in the 2006 AAP guidelines [15], viral testing is strongly encouraged in clinical trials and epidemiologic studies of bronchiolitis in order to identify potentially important differences in outcomes based on viral etiology. Although infection control measures such as isolation and cohorting are sometimes cited as justifications for viral testing, the 30% coinfection rate [11▪▪] may limit the effectiveness of these measures. Moreover, false negatives are possible, especially when rapid antigen testing is used [19,20], if the specimen is obtained by a nasal swab rather than a nasal aspirate [21], or if unsatisfactory specimens are obtained.

As part of a quality improvement effort at Santa Clara Valley Medical Center during 1 year of the MARC-30 study, the clinical care viral testing results (performed either at the referring emergency rooms/clinics or on the inpatient unit, using variable viral panels and techniques) were compared with the samples collected for study purposes, which were obtained via nasopharyngeal aspiration and tested for 16 viruses by polymerase chain reaction testing at Baylor College of Medicine [11▪▪]. Although small numbers and unpublished data, 23 of 25 (92%) patients who tested negative locally had positive testing for at least one virus in the MARC-30 laboratory at the Baylor. Furthermore, of the 16 patients who tested positive locally for a single virus, nine (56%) had a second virus detected at the Baylor. While either expansion or refinement of viral testing capabilities, or both, may reduce these types of false-negative results, there are associated costs of expanded testing, and no clear evidence that viral testing improves acute care.

Fever evaluation

Some infants with bronchiolitis have fever. As a result, laboratory tests are often ordered to help

evaluate for possible serious bacterial infections. The probability of bacteremia or bacterial meningitis in young infants with bronchiolitis is extremely low [22–24], making blood and cerebrospinal fluid testing low yield. The probability of urinary tract infection (UTI), on the other hand, is reportedly high enough (3–7%) to warrant consideration of urine testing. However, most of these studies have not required a positive urinalysis to confirm the diagnosis of UTI, as currently recommended by the AAP for infants 2 months to 2 years of age [25]. A portion of these UTIs may therefore simply represent colonization or asymptomatic bacteriuria, found in over 1% of healthy infants, and thereby lead to an overstated risk for UTI in this patient population [26,27].

THERAPEUTICS

In one of the first reviews on bronchiolitis, Wright and Beem [28] cautioned that 'the principle of *primum non nocere* should temper frustrated anxiety to do something – anything – to relieve severe dyspnea' and that an infant's 'energies should not be frittered away by the annoyance of unnecessary or futile medications and procedures.' Unfortunately, these admonitions from nearly 50 years ago appear to have gone largely unheeded.

Bronchodilators

The 2006 AAP bronchiolitis CPG discourages routine use of bronchodilators. However, this recommendation is qualified by the suggestion [15] that a 'carefully monitored trial… is an option.' Perhaps because this therapeutic door is left open, the administration of beta-agonists in bronchiolitis is still widespread. Even after the initiation of a quality improvement effort in 17 pediatric hospitals that was successful in reducing unnecessary therapies in bronchiolitis, infants continued to receive a mean of 4.3 doses of albuterol over the course of their hospitalization [3▪]. Over half of patients with bronchiolitis seen in emergency departments across the country continue to receive bronchodilators [17]. The most recent meta-analysis on the use of beta-agonists, which includes 28 trials involving 1912 patients, demonstrates that outpatient use does not reduce the rate of hospitalization and that inpatient use does not shorten LOS [29].

A concern about 'trials' of albuterol is that they may not be 'carefully monitored' as advocated by the AAP, and they are often accompanied by other interventions, such as antipyretics or intravenous fluids, which, when coupled with the benefits of time, may lead to clinical improvement that is interpreted as a 'response to albuterol.' For this reason, labeling a child with bronchiolitis as an 'albuterol responder' can be questionable depending on the other interventions occurring simultaneously.

Because the pathophysiology of bronchiolitis is characterized by bronchial wall edema and epithelial sloughing but not bronchospasm [30], the vasoconstrictive attributes of alpha-agonists should theoretically make them more effective than beta-agonists. Indeed, a meta-analysis of 19 trials involving 2256 patients demonstrated a small but significant reduction in hospitalization rates with epinephrine compared with placebo [relative risk 0.67, 95% confidence interval (CI): 0.50–0.89] and a shorter LOS with epinephrine compared with beta-agonists (mean: 0.28 days, 95% CI: 0.46–0.09 days), but not when compared with saline [31]. However, in a more recent trial involving 404 hospitalized infants, inhaled racemic adrenaline was no better than inhaled saline [32▪▪]. Interestingly, infants in this trial had a shorter LOS when either treatment (adrenaline or saline) was given 'on demand' rather than more frequently on a fixed schedule, supporting the notion that interventions of any kind can be harmful to a struggling infant with bronchiolitis [28]. A recent case report of an otherwise healthy infant who developed unstable ventricular tachycardia after a single dose of nebulized epinephrine [33] highlights the notion that no intervention is benign.

Hypertonic saline

The putative effect of hypertonic saline (HTS) in bronchiolitis is to absorb mucosal water in the bronchioles and enhance mucociliary clearance [34]. Although the most recent meta-analysis seems promising in terms of LOS reduction (mean: 1.15 days, 95% CI: 1.49–0.82) [35▪], the benefit appears to be concentrated in studies in which the mean LOS in both treatment arms was surprisingly long (5–7 days), which is less generalizable to United States populations, in which the mean LOS is closer to 2–3 days. Furthermore, trials published since this meta-analysis have demonstrated no benefit of HTS [36,37], a pattern that is all too familiar in bronchiolitis research [38].

Corticosteroids

Like HTS, early trials of steroids in bronchiolitis were encouraging [39]. However, the evidence continues to mount that steroids are ineffective [40▪], generating acceptance that corticosteroids are unnecessary and overused in bronchiolitis [2▪,15,41]. One large trial demonstrated no benefit of dexamethasone over placebo but did suggest that the combination of dexamethasone and racemic epinephrine reduced

hospitalization rates at day 7 [42]. Why this combination of therapies would be effective at day 7 but not in the short term remains unclear. Furthermore, this finding, which has yet to be replicated in other studies, did not retain statistical significance ($P = 0.07$) after adjustment for multiple comparisons [43].

There are some lingering questions about whether corticosteroids might be effective in patients who have rhinovirus infection [12], or more generally in those at risk for asthma (i.e. eczema or a first-degree relative with asthma), a population in whom a recent trial involving 200 patients found benefit of dexamethasone in terms of LOS reduction [44]. However, these findings are in contrast to those from a large study on corticosteroids in bronchiolitis [45], in which approximately two-thirds of the 600 patients studied were reported to have either eczema or a family history of asthma, and corticosteroids demonstrated no benefit in this subgroup. Similarly, in a slightly older population (10 months to 6 years) of children with virus-induced wheezing, systemic corticosteroids conferred no decrease in hospital LOS to the 124 children who were classified as being at high risk for asthma [46,47]. A more recent analysis of a small number of children with rhinovirus bronchiolitis demonstrated that there may be longer-term benefits of corticosteroids to reduce future wheezing [48▪], but the interpretation is based on a relatively small sample size and warrants repetition.

Respiratory syncytial virus immunoprophylaxis

Palivizumab is a monoclonal antibody used to limit the morbidity from RSV infections in high-risk infants (prematurity, chronic lung disease, and congenital heart disease). Although palivizumab has not improved RSV mortality rates, trials have demonstrated a modest reduction in hospitalization rates [49,50]. However, in the lower-risk groups (for whom prophylaxis continues to be given), the number-needed-to-treat (NNT) is in the range of 19–170, conferring an unfavorable cost-to-benefit ratio given the high cost of the drug [51]. Whether palivizumab prevents future wheezing episodes, as suggested by relatively preliminary data from two industry-sponsored trials [52,53], remains unproven. Clearly, the causal relationship between RSV or other viruses and the future development of asthma requires ongoing investigation.

SUPPORTIVE THERAPIES

The lack of benefit of pharmacologic agents leaves many practitioners wondering what, if anything, they can do for infants with bronchiolitis. General supportive measures include suctioning, hydration, and supplemental oxygen [15]. Infants with respiratory failure are generally managed in intensive care units with PPV [54].

Suctioning

Suctioning is a mainstay of both inpatient and outpatient bronchiolitis management, but this intervention has been poorly studied. While removal of mucus from a clogged nostril is intuitively an intervention that should not require a randomized trial to prove benefit, there are lingering uncertainties over technique and frequency. One recent study showed that LOS was prolonged in infants who received deep suctioning or who had long lapses (>4 h) between suctioning [55], suggesting that superficial suctioning may be the safest and most effective method.

Supplemental oxygen

The use of supplemental oxygen is another mainstay of inpatient management, although considerable controversy exists over when to initiate and discontinue oxygen therapy. Hypoxemia tends to drive hospitalization [7] and discharge [56,57] decisions, and oxygen saturation thresholds tend to vary substantially. The 2006 AAP bronchiolitis CPG recommends providing oxygen for saturations 'persistently below 90%' [15]. Some have voiced concern that cognitive impairment can occur even in children exposed to saturations in the 90–94% range [58], a provocative critique given a recent finding that a saturation threshold of 94% could prolong LOS in bronchiolitis by an estimated 22 h compared with a threshold of 90% [59]. However, the research cited by the authors [60] applies to children with sleep-disordered breathing and congenital heart disease, populations that are clearly quite different from infants with acute bronchiolitis. Even healthy young infants have been documented to have intermittent desaturations to <90% [61,62]. Therefore, continuous pulse oximetry may detect hypoxemia of unclear significance in young infants with bronchiolitis, thereby prolonging the hospitalization [56,57]. Avoiding continuous pulse oximetry in infants who are not on oxygen may help reduce excessive hospital days [2▪,15].

Another potential LOS reduction strategy is to send children with bronchiolitis home on oxygen, which may be both well tolerated and effective [63–65]. However, studies on this strategy were all conducted in high-altitude areas, where hypoxemia is more frequent if the same oxygen saturation thresholds are used. Survey data suggest that this

practice has not yet caught on in the rest of the United States [66].

In infants who are struggling to breathe, high-flow nasal cannula (HFNC) oxygen therapy is being used with increasing frequency. HFNC is appealing to many physicians as it appears to be less agitating to children than nasal continuous or bilevel positive airway pressure, and it may prevent endotracheal intubation in some cases of bronchiolitis [67–69]. Randomized trials of HFNC are greatly needed to assess efficacy and determine the optimal timing of initiation, and the safety profile needs further clarification [70].

CONCLUSION

The last few decades of bronchiolitis research have seen an abundance of studies evaluating various therapeutic strategies. Many therapies initially seem to hold some promise until proven ineffective by subsequent and generally larger trials, a phenomenon that may be attributed to publication bias [71]. Some questions remain over the possibility that specific subgroups of patients might benefit from a particular therapeutic intervention (e.g. children with prior wheezing, atopy, or infections with certain viruses such as rhinovirus [12,48▪,72]). In an ongoing multicenter study (website: www.wind study.org) supported by the National Institutes of Health, the MARC-35 investigators (website: www.emnet-usa.org) are examining multiple risk factors for the development of recurrent wheezing and eventual asthma in children hospitalized with bronchiolitis. It is possible that results from future trials of medications and interventions may vary based on newly identified subgroups of children. However, with an increasing emphasis on waste and escalating costs in our healthcare system [73], current efforts should focus on strategies aimed at decreasing tests and therapies that have demonstrated no benefit to date for children with bronchiolitis. As suggested in 1965 [28], clinicians should focus on not giving in to the 'frustrated anxiety to do something – anything – to relieve severe dyspnea' and limit their interventions whenever possible.

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Conflicts of interest

There are no conflicts of interest.

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