Acute Bronchiolitis and Croup

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Respiratory viruses are responsible for an extremely high proportion of all disease in young children presenting to medical services. Preschool children infected by one of these pathogens usually exhibit clinical illness with one or more upper airways manifestations such as coryza, pharyngitis, or otitis media. Extension of infection into the lower airways below the larynx most commonly causes "bronchitis," adding cough to the symptoms associated with the previously mentioned conditions. If the virus induces airways obstruction (most commonly through the induction of increased airways secretions and mucosal edema and/or bronchospasm), this obstruction may be manifest by increased work of breathing resulting in tachypnea and subcostal recession, gas trapping as manifested by hyperinflation, and noisy breathing caused by turbulent airflow.

The clinical phenotype of disease induced by a viral lower respiratory tract infection is determined by a number of factors, including the site of maximal inflammation, which in turn depends in part on the virus, the age of the infant or young child, and the existence of comorbidities such as atopic asthma. Although certain viruses classically are associated with certain disease phenotypes, such as parainfluenza with croup, respiratory syncytial virus (RSV) with acute bronchiolitis, and rhinovirus with exacerbation of asthma, any of the viruses can induce any of the clinical phenotypes.[1–5] The acute bronchiolitis associated with rhinovirus is clinically indistinguishable from that caused by RSV; RSV also is an important cause of croup and is responsible for a significant proportion of exacerbations of asthma in young children. The number of viruses known to target the respiratory tract continues to grow; viruses such as human metpneumovirus and human bocavirus have been added to the list of proven and likely respiratory pathogens.[5] As **Fig. 1** indicates for RSV (see **Fig. 1**A) and rhinovirus (see **Fig. 1**B), any of the conditions can be caused by any of the viruses, but the relative likelihood if a particular virus causing a particular condition varies with the virus.

One of the great challenges for those dealing with lower respiratory tract disease in children is that the lungs have a very limited repertoire of responses to acute or chronic insults. Increased airways secretions and cough are common to many conditions, such as acute or persistent bacterial infections, acute viral infections, untreated

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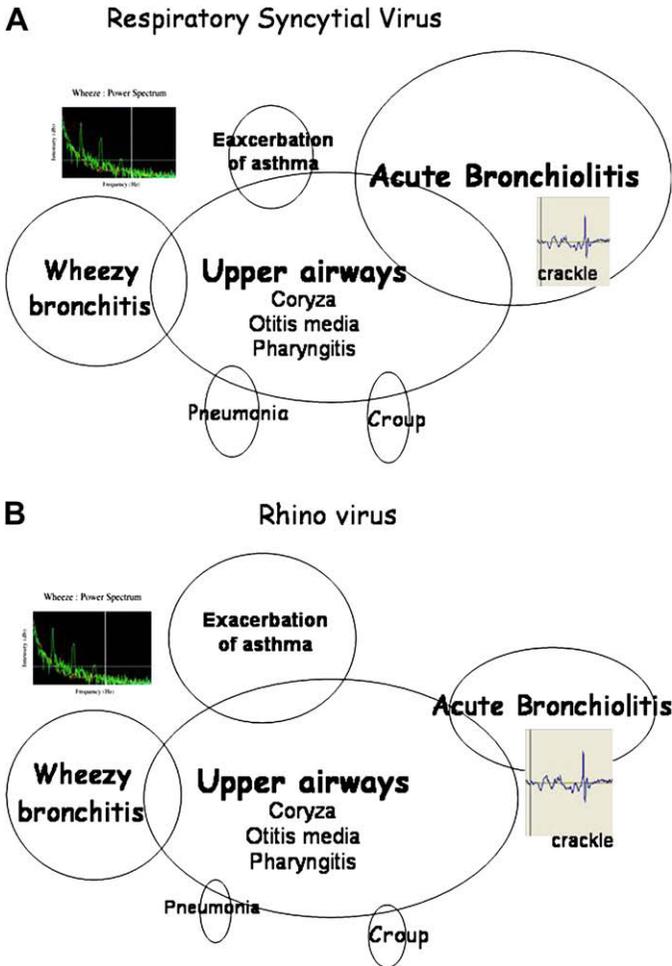*E-mail address:* m.l.everard@sheffield.ac.uk

Fig. 1. Phenotypes of respiratory illness caused by respiratory syncytial virus and rhinovirus.

asthma, and recurrent aspiration. In some individuals bronchoconstriction also can contribute to airways obstruction. Disease within the lower airways frequently leads to the generation of adventitial sounds. Secretions within the large airways can induce audible rattles and coarse airways noises[6,7] but also may contribute to the wheeze in patients experiencing an exacerbation of asthma or wheezy bronchitis. The lack of precision in using the term "wheeze" adds to the difficulties in this area. It is clear that parents and doctors use the term "wheeze" for a variety of respiratory, and indeed nonrespiratory, noises.[7–9] Because wheeze is a key symptom driving both diagnostic and therapeutic decisions, this imprecision is a major problem. Obstruction of distal airways with secretions may lead to the generation of inspiratory crackles (crepitations) heard on auscultation as units of alveoli pop open.

The lack of a simple test to distinguish conditions such asthma, wheezy bronchitis, and bronchiolitis means that care must be taken to describe accurately the phenotype of disease being experienced by an individual patient. This identification is a key step in ensuring that the patient receives optimal management. It must also be recognized that, even when the key clinical features have been considered carefully, it frequently

is impossible to provide an accurate diagnostic label. A preschool-age child with a clinically apparent viral upper respiratory tract infection, cough, and initial episode of wheeze may have a viral bronchitis with associated wheezing (wheezy bronchitis) or an exacerbation of asthma (see **Fig. 1**). There is no test to distinguish between the two conditions. Adding to the confusion, many clinicians label such an episode "acute bronchiolitis." The use of the term "virally associated wheeze" to describe wheezing associated with a viral infection in a nonasthmatic patient adds further unnecessary confusion, because the term includes both patients experiencing an exacerbation of asthma and patients who have wheezy bronchitis. Similarly, the term "reactive airways disease" does not help the clinician arrive at a more accurate diagnostic label. Although phenotypically the 13-month-old patient who has asthma may be indistinguishable form the 13-month-old patent who has wheezy bronchitis, there may be very important differences in some of the inflammatory components and the degree of bronchoconstriction. Thus a child who has wheezy bronchitis may look phenotypically like a child who has the first exacerbation of asthma; the airways inflammation dominated by neutrophils is likely to be very similar to that in a young child who has acute bronchiolitis characterized by widespread crackles. Thus two children with an obvious viral infection and prominent wheeze may look very similar but may respond quite differently to therapeutic interventions.

The lack of a definitive test and the resulting reliance on a clinical diagnosis adds a level of complexity to the consideration of the literature addressing lower airways conditions such as bronchiolitis. This complexity is compounded by lack of agreement between countries and indeed among clinicians within countries as to the definition of "acute bronchiolitis."

The clinical entity referred to as "acute viral croup" (acute laryngotracheobronchitis)[10] is less fraught with ambiguity, and this clarity probably accounts for the relative lack of controversy concerning this condition. Acute viral croup is identified more readily because, although the inflammation tends to involve the larynx, trachea, and large bronchi, the site of maximal airways obstruction generally is just below the larynx and thus is effectively extrathoracic. This extrathoracic positioning leads to airways obstruction that is maximal during inspiration: the negative pressure generated during inspiration leads to narrowing of the upper airway and the extrathoracic portion of the trachea. As a result, a RSV infection causing significant edema in the upper trachea produces the clinical picture of croup. When the inflammation is predominantly distal, it may cause acute bronchiolitis or an exacerbation of asthma with airways obstruction being maximal during the expiratory phase of the respiratory cycle. The differential diagnosis of a child who has an apparent viral infection, barking cough, and inspiratory stridor is quite different from that of the many conditions causing obstruction in the distal airways, and it is a condition that is much easier to characterize on clinical grounds.

ACUTE BRONCHIOLITIS
Evidence-Based Guidelines

At least two comprehensive evidence-based guidelines covering the diagnosis, management, and prevention of acute bronchiolitis have been published in the past 18 months. Both the American Academy of Pediatrics (AAP)[11] and the Scottish Intercollegiate Guideline Network (SIGN) guidelines[12] from Scotland used rigorous evidence-based methodology, including a comprehensive review of the literature, the use of relevant systematic reviews, consultation, and peer review. Reassuringly, in most respects, they have reached the same conclusions and reflect the author's practice based on a review of the literature (**Table 1**). They state that diagnosis should be based

Table 1
Diagnosis and management of acute bronchiolitis and croup

Practice	Recommended/Not Recommended	Strength of Recommendation[a]	Quality of Supporting Evidence
Acute bronchiolitis			
Diagnosis and assessment			
Diagnosis on basis of history and examination	Recommended (see text)	Moderate	Low
Transcutaneous oxygen saturation	Recommended	Strong	Moderate
Admission based on severity and risk factors	Recommended	Strong	Moderate
Virologic testing (for infection control)	Recommended	Weak	Low
Hematology/biochemistry	Not recommended	Strong	Moderate
Chest radiograph	Not recommended	Strong	Moderate
Interventions			
Oxygen prescription for transcutaneous oxygen < 92%	Recommended	Weak	Low
Prevent dehydration and moderate fluid restriction	Recommended	Strong	Moderate
Beta-agonists	Not recommended	Strong	Moderate
Adrenaline	Not recommended	Strong	Moderate
Routine antibiotics	Not recommended	Strong	High
Inhaled corticosteroids	Not recommended	Strong	Moderate
Oral corticosteroids	Not recommended	Strong	Moderate
Physiotherapy	Not recommended	Strong	Low
Antiviral therapy (ribavirin)	Not recommended	Strong	Moderate
Antileukotriene therapy	Not recommended	Strong	Moderate
Infection control			
Hand decontamination	Recommended	Strong	Strong
Gloves and gowns	Recommended	Strong	Moderate
Croup			
Diagnosis and assessment			
Clinical diagnosis	Recommended	Strong	Moderate
Admission based on clinical assessment of severity and risk factors	Recommended	Strong	Moderate
Transcutaneous oxygen measurements	Not recommended	Weak	Low
Virology	Not recommended	Strong	Moderate
Hematology/biochemistry	Not recommended	Strong	Moderate
Radiology	Not recommended	Strong	Moderate
Interventions			
Systemic (or nebulized) corticosteroids for moderate and severe croup	Recommended	Strong	High

Table 1
(continued)

Practice	Recommended/Not Recommended	Strength of Recommendation[a]	Quality of Supporting Evidence
Nebulized adrenaline for moderate to severe croup	Recommended	Strong	Moderate
Heliox	Not recommended	Weak	Low
Humidification/steam	Not recommended	Strong	Moderate

Quality of supporting evidence regarding treatment depends entirely on whether there are important subgroups within the spectrum of disease covered by the term "acute bronchiolitis."

[a] Grading is based on the GRADE approach in Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.

on clinical assessment and that no test is helpful in making the diagnosis. Assessment of the severity and need for admission to hospital or intensive care also should be based on clinical grounds, including assessment of age and risk factors such as prematurity, chronic lung disease, or significant cardiac disease. Pulse oximetry is helpful in identifying hypoxia, but the two guidelines agree that there is little evidence to support the use of any one or group of features as a means of predicting progression of the illness. Investigations such chest radiographs and blood tests are not indicated unless the illness is atypical or particularly severe. Management consists of good supportive care, which may include intensive supportive care. Management has not changed essentially since Reynolds and Cook[13] stated in 1963 that "oxygen is vitally important and there is little evidence that any other therapy is consistently or even occasionally useful." Supportive care includes administration of fluids sufficient to prevent dehydration but restricted to prevent problems with hyponatremia caused by inappropriate antidiuretic hormone secretion. Both guidelines are clear that there is no proven pharmacologic treatment other than oxygen and that pharmacologic agents such as α- or β-agonists, inhaled or systemic corticosteroids, ribavirin, and antibiotics should not be used routinely. The use of good infection control measures is key to preventing nosocomial spread within pediatric units. Hand decontamination, preferably with an alcohol-based rub, is the most important measure. Gloves and gowns probably provide further benefit, and education of staff, relatives, and visitors has been shown to have value. Both guidelines state that monoclonal prophylaxis may be given to infants at risk, but pharmacoeconomic issues lead to differences in the strength of the recommendation. Neither set of guidelines mentions a role for interventions to prevent future morbidity, but at present there is no evidence that any treatment, including inhaled or systemic steroids[14] and antileukotriene antagonists administered during or immediately after the illness, has any impact on future morbidity.

The guidelines grade the strength of many of these recommendations as high because they are based on a number of systematic reviews, many of which were undertaken as part of the Cochrane Collaboration.[15–19] There are, however, some subtle, potentially important differences within this broad consensus that infants and young children should be managed conservatively, avoiding the unnecessary tests and therapies that do not have any effect. These differences include a trial of α- and β-agonists, the indications for using supplemental oxygen, the use of monoclonal antibodies in the prevention of RSV disease, the value of viral testing in helping prevent

nosocomial spread, and, perhaps most important of all, the diagnosis of the condition. Indeed both sets of guidelines seem to have some internal contradictions relating to some of these issues.

It also is of interest that these guidelines do not reflect practice in many countries, and there is good evidence that the introduction of similar guidelines in a variety of countries has had little effect on practice, particularly recommendations relating to pharmacologic agents, which still are widely prescribed.[20–23] In part this lack of effect may result from the well-known difficulty of changing clinical practice, in part because clinicians feel that they should provide treatment even though there is little evidence to support the practice. Principally, however, this lack of effect probably results from the difficulties involved in agreeing about what "acute bronchiolitis" is. The following section considers possible reasons for the ongoing controversies that exist in this area.

Bronchodilators Should Not Be Used Routinely But Remain an Option

Although the AAP guideline states under recommendation 2a that bronchodilators should not be used routinely in the management of bronchiolitis (recommendation: evidence level B; randomized, controlled trials (RCTs) with limitations; preponderance of harm of use over benefit). It then almost immediately makes recommendation 2b: that a carefully monitored trial of α-adrenergic or β-adrenergic medication is an option. Inhaled bronchodilators should be continued only if there is a documented positive clinical response to the trial using an objective means of evaluation.

Although all national guidelines state that there is no evidence that any pharmacologic agent is useful in the treatment of acute bronchiolitis, the position advocated under recommendation 2b reflects the practice of many clinicians around the world, and many publications have noted that compliance with the recommendation not to use pharmacologic agents is poor.[20–23] This apparent discrepancy within a guideline (and the lack of compliance with guidelines) probably reflects the lack of consistency and specificity in the use of terms such as "acute bronchiolitis," "asthma," and "wheezy bronchitis" by clinicians, be they primary care physicians or tertiary specialists. As with all systematic reviews, the conclusions that can be drawn are only as good as the quality of data available for assessment. Reynolds and Cook13 noted more than 45 years ago that

> Much of the confusion about the management of bronchiolitis results from the fact that are probably two groups of patients: (1) those with obstructive disease resulting entirely from infection, thickening of the bronchiolar walls and intrabronchial secretions and (2) those with a pre-disposition to asthma who develop obstruction as a result of both inflammation and bronchospasm. The two groups cannot be readily distinguished on clinical grounds, it would appear that most patients fall in the first group.

If data are derived from different studies that have different population of patients or from studies that contain mixed populations, the results at best may be mixed and at worst are misleading.

Implications of the Lack of Precision in the Definition of Acute Bronchiolitis

When assessing the literature referring to infants who have acute bronchiolitis, it is important to understand that the publication may refer to one of at least two quite distinct phenotypes. In the United States and a number of European countries, the term is used to describe a young child or infant who has an apparent viral respiratory tract infection and a first episode of wheeze, but in the United Kingdom, Australia, and some

parts of Europe, the term refers to an infant who has an apparent viral respiratory tract infection with lower airways obstruction accompanied by widespread crackles (crepitations). The later definition recognizes that such infants may wheeze occasionally or intermittently during the disease, but widespread crackles are the key diagnostic feature. The presence of crackles indicates that maximal obstruction is at the level of the distal airways (bronchiolitis) with terminal unit opening suddenly during inspiration and resulting in the discontinuous adventitial sounds. Interestingly, countries using this second definition have much better compliance with the guidelines suggesting that pharmacologic agents are of little value.[24]

Previous studies have indicated that the inflammatory process in patients who have RSV-induced ''UK bronchiolitis'' is dominated by an intense neutrophilic influx into the airways.[25] This influx seems to be driven by very high levels of cytokines such as interleukin-8[26] and inhibition of polymorphonuclear neutrophil (PMN) apoptosis.[27] A PMN response seems to be characteristic of the response to this and other respiratory viruses.[28] PMN products such as human neutrophil elastase and myeloperoxidase are potent inflammatory mediators driving mucus secretion, airways edema, and cough. At present it is not known whether the PMNs contribute significantly to elimination of the virus, and it is possible that the virus utilizes this response to assist in dissemination to other subjects. In such a context, standard interventions used to treat older patients who have asthma might well prove to be ineffective. Corticosteroids are believed to have little effect on neutrophilic airways inflammation, whereas β-agonists are unlikely to have much effect if bronchoconstriction is not a prominent feature.

As noted previously and as illustrated in **Fig. 1**, it is possible that a child who has an apparent viral infection with a first episode of wheezing (''American bronchiolitis'') may be experiencing a first exacerbation of asthma or may have ''wheezy bronchitis.'' Epidemiologic data suggest that, in patients who have ''wheezy bronchitis,'' pre-existing factors, which may include relative airways size,[29] predispose these children to suffering one or more episodes of airways obstruction induced by a viral lower respiratory tract infection that is accompanied by wheeze. This tendency to wheeze with a viral lower respiratory tract infection declines in the preschool years. It is probable, but not proven, that these children have a pattern of inflammation similar to that seen in those who have ''UK bronchiolitis'' but that the manifestations are different because of lung growth and factors such as the development of pores of Kohn. Hence, phenotypically these patients may be indistinguishable from a child of similar age who has an exacerbation of asthma, but in terms of inflammation they are much closer to patients who have ''UK acute bronchiolitis.'' Hence two children who look very similar may react very differently to pharmacologic agents.

Because the type of patient included in any cohort or therapeutic study influences the results obtained, this semantic issue may be key to understanding why there is such controversy in this field. A group selected on the presence of wheeze without crepitations is likely to include a sizable group of asthmatics, but epidemiologic data indicate that asthmatics still will represent a minority of the patients. Consequently any treatment effect that might be present if ''pure'' asthmatics were included might be lost if there is little or no benefit in the wheezy bronchitis groups. Similarly, if a substantial proportion of the recruited subjects are ''asthmatics,'' this population might be sufficient for a study to show a statistically significant benefit, even if there is no clinical benefit in the ''nonasthmatic'' subjects. The danger is that such a conclusion might be generalized to the whole population of young, acutely wheezy children.

The AAP guidelines notes that

Overall, results of the meta-analysis indicated that, at most, 1 in 4 children treated with bronchodilators might have a transient improvement in clinical score of unclear clinical significance. This needs to be weighed against the potential adverse effects and cost of these agents and the fact that most children treated with bronchodilators will not benefit from their use. Studies assessing the impact of bronchodilators on long-term outcomes have found no impact on the overall course of the illness.

Such results would be consistent with the proposal that a significant minority of those in whom wheeze, in the absence of crackles, is the prominent symptom is likely to have a virally induced exacerbation of asthma. An alternative explanation, however, is that, as in any study, some patients will improve while others may remain static or indeed deteriorate before improving, and that post hoc subgroup analysis provides spurious evidence for a subgroup of responders.

Clinicians would not withhold β-agonists from an older child experiencing a virally induced exacerbation of asthma, even though the bronchodilation achieved is limited (in contrast to an asthmatic with poor control, in whom large changes in lung function may be observed)[30] and even though bronchodilator per se does not have a significant impact on the course of the illness or duration of hospitalization. The bronchodilator provides modest, temporary relief while waiting for the corticosteroids to take effect.

Acute Bronchiolitis—Diagnostic Recommendations from Guidelines

In their review Reynold and Cook[13] noted that pediatricians recognized that bronchiolitis is the most common acute lower respiratory tract infection necessitating hospitalization in infants less than 1 year of age, but the lack of a clear definition of the illness has been associated with a marked confusion concerning its management. This problem is reflected 45 years later in the AAP guidelines that define bronchiolitis as

a disorder most commonly caused in infants by viral lower respiratory tract infection. It is the most common lower respiratory infection in this age group. It is characterized by acute inflammation, edema, and necrosis of epithelial cells lining small airways, increased mucus production, and bronchospasm.

Although most of these features have been confirmed by histology in the most severely affected patients who die from the condition, the inclusion of bronchospasm is difficult to justify, particularly because a key recommendation is that "bronchodilators should not be used routinely in the management of bronchiolitis."

The guidelines recommend that the diagnosis and assessment should be based on history and physical examination. They note:

Most clinicians recognize bronchiolitis as a constellation of clinical symptoms and signs including a viral upper respiratory prodrome followed by increased respiratory effort and wheezing in children less than 2 years of age. Clinical signs and symptoms of bronchiolitis consist of rhinorrhea, cough, wheezing, tachypnea, and increased respiratory effort manifested as grunting, nasal flaring, and intercostal and/or subcostal retractions.

There is no mention of crackles in this section on diagnosis and assessment, although the introduction contains a similar paragraph that includes the sentence, "Signs and symptoms are typically rhinitis, tachypnea, wheezing, cough, crackles, use of accessory muscles, and/or nasal flaring."

Similarly, the SIGN guidelines are not entirely internally consistent with their definition of the condition stating that bronchiolitis is a condition characterized by "fever, nasal discharge, a dry wheezy cough and on examination there are widespread fine crackles and/or high pitched expiratory wheeze." The guidelines then comment that

In the UK, crackles on auscultation are considered to be the hall mark of the condition. Infants with no crackles and only transient early wheezing are usually categorised as having viral-induced wheezing and not bronchiolitis. American definitions place much greater emphasis on the inclusion of wheeze in the definition. This makes it difficult to extrapolate from American research. Or vice versa!

Does the Definition of Acute Bronchiolitis Matter?

A study of patients admitted to hospital with an RSV infection demonstrated that the host response is an important determinant of both the phenotype of the acute illness and subsequent respiratory morbidity.[31] At presentation the patients were ascribed the phenotypes "RSV acute bronchiolitis" (bilateral crepitation) or "RSV wheeze" (wheeze but no crepitations), and the children were followed to 3 years of age. The group with wheeze was older at the time of the acute illness and had significantly higher rates of personal atopy than either the controls or the patients who had RSV bronchiolitis. (The patients who had RSV bronchiolitis, in turn, had slightly lower levels of atopy than controls). At 3 years of age the wheezing group had much higher levels of respiratory morbidity and use of inhaled corticosteroids. This finding suggests that the wheezing cohort was made up of two different groups, despite their sharing the same phenotype. Although there was some increase in respiratory morbidity, mainly with viral infections, in the patients who had RSV bronchiolitis, they did not have higher levels of inhaled corticosteroid use. These data suggest that it is not the virus per se but host factors (including immunologic, inflammatory, and physiologic factors) that determine the phenotype of the acute illness and the pattern of subsequent respiratory morbidity. Other studies have tried to distinguish RSV bronchiolitis (crackles) from RSV wheeze prospectively and have found differences in the inflammatory process.[32] These factors also influence the therapeutic effect, if any, of pharmacologic agents.

Until there is a simple test to diagnose asthma other than its being a condition that improves significantly with asthma treatment (as manifested by objective bronchodilation in response to β-agonists or a significant change in morbidity in response to inhaled corticosteroids) and reoccurs if the treatment is withdrawn—a position advocated by both the British SIGN/British Thoracic Society[33] and GINA guidelines[34]—the AAP recommendation 2b is likely to remain reasonable, if wheeze is considered the key feature of bronchiolitis.

Potential Importance of Choosing the Appropriate End Points

As noted earlier, the inclusion of a mixed population in a study of a pharmacologic agent may result in missing valuable treatment effects in a minority. Under recommendation 2b, the reviews noted that a minority of patients seemed to have a "transient improvement in clinical score of unclear clinical significance." In this setting the clinical benefit may be missed because of the patient's inability to communicate. The use of β-agonists would not be recommended in older children if their use did not lead to more rapid discharge compared with systemic corticosteroids alone. The transient and often small improvement in lung function observed when treating a patient who has a significant exacerbation of asthma is still appreciated by the patient while waiting for the corticosteroids to take effect.

Another example of a potential problem in developing evidence-based guidelines is illustrated in a letter criticizing the AAP guidelines for its recommendation that supplemental oxygen be administered if the patient's transcutaneous oxygen readings fall consistently below 90%. In the SIGN guidelines, a threshold value of 92% is suggested. Neither level seems to be associated with adverse outcomes in the short term. Extrapolating from the treatment of other conditions, it has been suggested that accepting levels as low as 90% may be associated with subtle but possibly important long-term neurodevelopment problems.[35] Because no study has ever addressed this issue, there is no means of addressing this potential problem without undertaking a long-term study. Clearly long-term outcomes are very important, as illustrated by the concerns regarding the possible link between the use of postnatal corticosteroids to treat chronic lung disease and neurodevelopmental outcomes.

Summary

Two rigorous evidence-based guidelines have come to very similar conclusions, but there are important, if subtle, differences that seem to relate to the precision with which terms such as "acute bronchiolitis" are used. The strength of the recommendations depends entirely on the robustness of the entry criteria in the studies subject to systematic reviews. Although the guidelines grade the evidence behind most recommendations as "good," being based on RTCs, this grading presupposes that the subjects included are a homogeneous, "clean" population, an assumption that may not be valid.

Presumably because the AAP committee working on the guideline recognized that this is a definitive, evidence-based guideline with potential limitations beyond their control, they inserted the prudent statement,

This clinical practice guideline is not intended as a sole source of guidance in the management of children with bronchiolitis. Rather, it is intended to assist clinicians in decision-making. It is not intended to replace clinical judgment or establish a protocol for the care of all children with this condition. These recommendations may not provide the only appropriate approach to the management of children with bronchiolitis.

CROUP

Viral croup is a common clinical illness most commonly seen in preschool children, generally between 6 months and 5 years of age. The incidence peaks in the second year of life, and around 15% of children experience at least one episode. Although the infection involves the larynx and large central airways, the airways obstruction, when present, occurs during inspiration with the maximal narrowing occurring in the upper, extrathoracic, trachea.[10] As with all viral infections, the severity ranges widely, from an irritating barking cough to severe, life-threatening airways obstruction. The management of croup has been transformed during the past 20 years, in large part because of a systematic review that reviewed earlier small studies assessing the potential role of steroids in the management of croup.[36] Many pediatric pulmonologists previously had conclude that steroids had no place in the management of this conditions. This conclusion was based on small, underpowered studies; some of these studies had found a trend toward benefit, but none had demonstrated any clear, statistically significant benefit. The meta-analysis undertaken by Kairys and colleagues,[36] however, showed clearly that this opinion should be reconsidered. A series of studies, first in the ICU[37] and then in the emergency room, followed,

indicating that corticosteroids, administered orally, parentally, or inhaled, led to a rapid improvement in the clinical status of patients who had croup.[38] Many centers have reported that admissions to hospital and intensive care have fallen dramatically with this approach,[39] although the use of corticosteroids does not inevitably prevent progression and even death.[40] More recent studies have considered the use of corticosteroids even for milder disease managed in the community. Interestingly, despite the systematic review and evidence from the ICU, one of the first large emergency room studies was rejected by a major journal largely because one reviewer believed that such a study was "unethical as everyone knew steroids did not work in croup" (G. Geelhoed, personal communication, 1998).

Assessment

Diagnosis

The diagnosis of acute viral croup is based on clinical assessment. The differential diagnosis in patients who have moderate to severe airways obstruction with stridor includes any condition that might cause acute narrowing at the larynx or upper trachea.[10,40,41] Traditionally the most important differential diagnosis has been acute epiglottitis, although the incidence of this condition has fallen dramatically with the widespread use of vaccination against type b *Haemophilus influenzae.* It still is important, however, to consider the possibility that it a child may have epiglottitis, which can occur because of vaccine failure or infection with other organisms. Laryngeal foreign bodies, bacterial tracheitis, retropharyngeal abscess, and angioedema are other important conditions to consider. Particularly severe symptoms or presentation at a very young age should raise the possibility of an underlying problem such as subglottic stenosis. It is important to ensure that the diagnosis is correct, because several of these conditions require urgent and distinct forms of treatment.

Severity

Children who have stridor should be kept as calm as possible, and medical staff should avoid upsetting the child. Crying generates large negative intrathoracic pressures that exacerbate the collapse of the narrowed tracheal lumen and can provoke a vicious circle of increased distress caused by the increased difficulty breathing that leads to further crying and continued excessive airways narrowing. A number of croup scores have been devised, principally for the research setting. The most widely used is the one reported by Westley,[42] which has been used in a number of therapeutic trials. Although a number of emergency departments use these scores, evidence is lacking that the use of a scoring system improves treatment decisions or outcomes. It is argued consistently that clinical assessment of airways obstruction, which includes the patient's general appearance as well as the presence of stridor and recession, is critical, as is regular, repeated reassessment until the patient is clearly improving.[10,41,43] This approach can be viewed as a consensus position based on expertise rather than on objective studies. Pulse oximetry is widely used but is of limited significance, because values are normal or minimally affected in almost all infants. Low oxygen saturations caused by narrowing of the extrathoracic trachea, as seen in croup, is evidence of very severe narrowing. In distal airways obstruction, as seen in bronchiolitis, the huge number of airways within each generation means that hypoxia can be treated with supplemental oxygen without placing the patient at risk of catastrophic obstruction. In upper tracheal obstruction, however, the lumen narrows markedly before the child becomes hypoxic, and the patient then is at risk of catastrophic cardiorespiratory arrest. Therefore hypoxia caused by croup is an indication that the child should be transferred safely to an ICU or high-dependency

unit. Conversely, patients who have mild disease may have evidence of mild hypoxia caused by concurrent involvement of the lower airways tract.

There is no evidence that any other investigation is helpful, and indeed investigations such as blood tests or radiographs, which may cause distress, can exacerbate the situation significantly, both in croup and in conditions that can mimic croup, such as epiglottitis.

Treatment

As noted earlier, the key change in the management of croup has been the widespread administration of corticosteroids, by a variety of routes, to patients who have moderate or severe croup (see **Table 1**). There is increasing evidence that a single dose of a corticosteroid may have benefits even in patients who have relatively mild symptoms, such as mild stridor and recession only when upset. It is widely believed that a single dose has no significant long-term effects, so the risk–benefit ratio favors the use of such agents. The Cochrane review addressing this issue[38] was updated most recently in 2004 and found significant benefits in a range of outcomes, including improvements in severity scores at 6 hours, reduced re-presentation and readmissions, shorter length of stay in those admitted to hospital, and a reduction in the use of epinephrine. The review was unable to show an effect on the need for intubation. When assessing the relative effectiveness of oral and inhaled therapy, the reviewers were unable to identify a clear benefit of one method of administration over the other, although there was a strong trend for inhaled fluticasone delivered via spacer to be less effective than dexamethasone or nebulized budesonide. The reviewers concluded, "In the absence of further evidence, a single oral dose of dexamethasone, probably 0.6 mg/kg, should be preferred because of its safety, efficacy, and cost-effectiveness. In a child who is vomiting, nebulized budesonide or intramuscular dexamethasone might be preferable." Studies to define optimal doses are on going, with a number of studies suggesting that lower doses are as effective as higher ones.[44,45]

The other pharmacologic agent shown to have a benefit is epinephrine. There is no meta-analysis, but a number of RTCs consistently have indicated that there are clinical benefits.[46–52] Although early studies reported using racemic adrenaline, this drug has not been shown to be superior to L-epinephrine.[46] Unlike corticosteroids, this form of therapy does not alter the natural history of the illness but does reduce the severity of symptoms transiently, probably through vasoconstriction leading to reduced hyperemia and edema. The onset is rapid (< 30 minutes), but the duration of efficacy is short (< 2 hours). The standard dose seems to be 0.5 mL/kg body weight nebulized up to a maximum of 5 mL (10 kgs or greater). Although there is good evidence that epinephrine can reduce symptom scores temporarily, there is no clear guidance as to when it should be used. It is used frequently to provide symptomatic relief in patients who have moderate to severe symptoms while waiting for corticosteroids to take effect. Tachycardia and pallor are relatively common; more serious side effects seem to be rare,[53] although a case of myocardial infarction has been reported following frequent administration in a young child who had severe obstruction.[54] Potentially, the most significant problem is that frequent use of epinephrine could mask a significant deterioration in the underlying obstruction.

Heliox (70/30 helium/oxygen mixture) also has been advocated as a therapeutic intervention in patients who have severe croup, on the basis that its lower density, as compared with air, improves gas flow. A small, double-blind, randomized trial comparing heliox with nebulized epinephrine in patients already receiving systemic steroids did not identify any benefit of heliox over epinephrine.[55] Unless further data

support this form of therapy, it is unlikely that heliox can be recommended, given the increased complexity of its use.

A recent Cochrane review found no evidence to support the use of humidified air to treat children who have croup,[56] even though this practice has been widely advocated for many decades. The review identified only three small studies based in the emergency department and none in primary care. A subsequent study again found no benefit from humidification, and this practice cannot be recommended.[57]

Summary

Although there is little current controversy regarding the management of croup, assessment remains largely clinical. The natural history seems to be modified by a single dose of steroids. Although there is a benefit from oral, nebulized, or intramuscular treatment, oral dexamethasone seems to be the most acceptable method for most patients. Temporary benefit can be derived from the use of nebulized epinephrine, and studies indicate that patients can be discharged within 3 to 4 hours after the last dose, providing there is no deterioration after the effects of epinephrine have worn off and that the patient is continuing to improve.

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