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24 Bronchiolitis

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Epidemiology

Bronchiolitis is the most common lower respiratory tract infection in children. The condition forms part of the spectrum of viral lower respiratory tract infection that includes bronchiolitis, viral pneumonia, and viral-induced wheeze. In polar hemispheres (north and south), bronchiolitis is a seasonal disease, dominating winter months, with a peak over 6 to 8 weeks around the winter solstice. In tropical climates, the disease is associated with rainy months and is seasonally more dispersed.[1] Climate and environment appear to influence both season and severity.[2,3]

Bronchiolitis is diagnosed clinically by integrating characteristic but variable signs and symptoms across a broad age range, though the majority of cases occur in children under 1 year of age. The condition can be caused by any respiratory virus and has a wide spectrum of disease severity.[4]

A "classic" case would be an infant aged 3 to 5 months of age[5] who develops coryza and over the subsequent 3 to 4 days has increased difficulty with breathing, and consequent inability to maintain adequate oral feeding. Wheeze or crackles can be heard on auscultation. Improvement occurs by days 5 to 7, though a characteristic harsh cough may persist for 21 days or more.[6,7]

While the diagnosis often appears straightforward, the wide range of disease severity across a skewed but broad age range and the need for clinical diagnosis (with associated inconsistency) creates difficulty in establishing precise data.[8] In addition, while bronchiolitis is a clinical diagnosis applied to any infecting agent, the majority of data available relate to bronchiolitis caused by respiratory syncytial virus (RSV) infection; and within RSV bronchiolitis is a focus on those at high risk, in particular, those born prematurely. Reference to these groups synonymously with bronchiolitis can make interpretation of epidemiological data difficult and may reduce the understanding of bronchiolitis caused by non-RSV and in lower risk patients (particularly children born at term).

POPULATION RISK FOR BRONCHIOLITIS ASSOCIATED WITH ALL RESPIRATORY VIRUSES

There are only limited estimates of population risk for bronchiolitis associated with all respiratory virus infections, but approximately 40% of infants are affected by bronchiolitis in the first year of life.[9] In the United Kingdom, using primary care databases, the 1 year incidence of children given a specific diagnosis of bronchiolitis is 58 to 65 per 1000 children,[8,10] rising to 204 per 1000 when a broader definition of bronchiolitis was used to capture potential cases.[8] This study highlights that in children with typical lower respiratory tract signs and symptoms, clinicians may not ascribe the discrete diagnosis of bronchiolitis; a finding also found in other countries such as Spain[11] and across health care systems,[12] with evidence that a diagnosis of bronchiolitis is more likely to be made in secondary than primary care. The hospital admission rate for bronchiolitis in children without high-risk conditions is 1.9% in the United States using coded hospital data,[13] showing a decline from 2.7% in the period 2000–2009. In contrast, UK data suggest that admission rates are continuing to increase over time (to 4.0% in 2011).[14] Of those admitted to hospital, 85% are born at term and 15% are born preterm.[15] Additional factors also place children at higher risk of admission including, age (<3 months), male sex, being bottle-fed, multiple birth, and family smoking. Rates of admission for infants with a diagnosis of bronchiolitis can vary up to threefold across hospitals in the same country.[14] Duration of admission is also highly variable within countries and internationally.[16]

Mortality for bronchiolitis is low[17]; United States 0.03% overall, with an adjusted odds ratio (OR) of 0.25 for mortality in children less than 1 year of age without previous health condition and primary diagnosis of bronchiolitis.[13] Admissions to intensive care have remained constant over time[14] although related costs are increasing.[13]

POPULATION RISK FOR RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS

RSV infects 69% to 98% of infants in the first year of life.[18,19] The rapid development of vaccines and treatment therapies for RSV has added impetus to the need to better define the burden of RSV disease. Globally there are an estimated 33.8 million cases of RSV lower respiratory tract infection each year in children under 5 years of age, resulting in 3.4 million admissions to the hospital and 66 to 199 thousand deaths (with the majority in low- and middle-income countries).[20]

In the United States an estimated 20% of children will attend primary care each year with RSV bronchiolitis, and up to 7% attend an Emergency Department (ED).[21] Admission to hospital with RSV bronchiolitis is typically around 2.4% of all infants,[15,22] though in previously healthy term infants, the admission rate to hospital with RSV bronchiolitis can be as low as 0.7%.[23]

HIGH-RISK POPULATION FOR BRONCHIOLITIS ASSOCIATED WITH ALL RESPIRATORY VIRUSES

In infants who are born preterm at 32 to 35 weeks' gestation, 48% will develop bronchiolitis and 6% require admission to the hospital.[24] The risk of bronchiolitis is increased in a range of conditions compared with term infants, including preterm birth (respiratory rate [RR] 1.89), cystic fibrosis (RR 2.45), congenital heart disease (RR 3.35), chronic lung disease (RR 1.61), immunodeficiency (RR 1.73), Down syndrome (RR 2.53), and cerebral palsy (RR 2.43).[25,26]

ABSTRACT

Acute viral bronchiolitis is a common viral lower respiratory tract infection in young children. Most typically caused by respiratory syncytial virus in 70% of cases, the condition lasts for 4 to 7 days, with a prolonged cough in many. Children with comorbidity, particularly those born prematurely or with significant congenital heart disease, are at risk of more severe disease. Nasal obstruction progresses over 3 to 4 days to difficulty with feeding and increased work of breathing with hypoxemia. Crackles and/or wheeze may be auscultated. Apnoea may be a presenting sign in those less than 3 months of age. Viral load is highest at peak of symptoms and in those with more severe disease. Approximately 2% to 3% of all children are admitted to hospital with bronchiolitis. The differential diagnosis may include bacterial pneumonia, congenital lesions of the lung or heart, or an interstitial lung disease. There are no effective treatments, and admission is for feeding support (by nasogastric or intravenous fluids) or treatment of hypoxemia. Critical care support is required for some infants experiencing respiratory failure, though mortality rates remain unchanged. Practice within and between countries varies significantly and alignment of practice is a common goal of guidelines. Vaccines for RSV are in advanced development, as are several antiviral therapies for RSV. In most children, acute symptoms improve within 5 to 7 days and cough by 2 weeks. Recurrent wheeze is common following acute bronchiolitis and a good association with a diagnosis of asthma in childhood.

KEYWORDS

bronchiolitis
viral lower respiratory tract infection
wheeze
respiratory syncytial virus

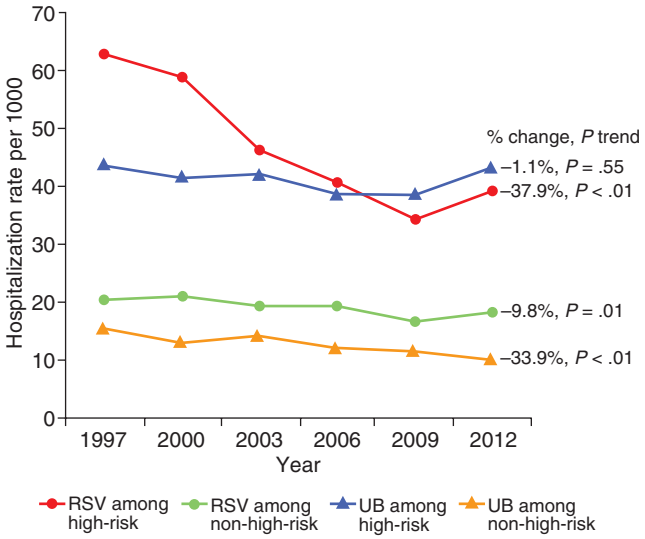

Fig. 24.1 Rate of hospitalizations due to respiratory syncytial virus (RSV) or unspecified bronchiolitis (UB) according to high-risk status in the United States Kids Inpatient Database, 1997–2012. (Doucette A, Jiang X, Fryzek J, et al. Trends in respiratory syncytial virus and bronchiolitis hospitalization rates in high-risk infants in a United States Nationally Representative Database, 1997–2012. *PLoS One.* 2016;11(4):e0152208.)

HIGH-RISK POPULATION FOR RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS

For infants born ≤ 32 weeks gestation, 75% of infants will have a lower respiratory tract infection in the first year of life, with 35% RSV positive and 40% RSV negative; of these infants, 41% of RSV positive will be admitted to the hospital versus 18% of RSV negative.[27] Recent studies suggest that hospitalization rates for high-risk infants due to RSV are reducing over time and are now similar to those for RSV negative, possibly as a result of improvements in neonatal care or immunoprophylaxis in high-risk groups (Fig. 24.1).[28,29] Risk of death is much higher amongst high-risk groups who are RSV positive, including preterm (1.2%), congenital heart disease (5.2%), and bronchopulmonary dysplasia (7.0%).[17]

Etiology

Bronchiolitis has a viral etiology, with RSV the most common cause, reported in 43% to 75%[30,31] of cases. Other viruses associated with bronchiolitis are human rhinovirus (18%), influenza, coronavirus, human metapneumovirus, adenovirus, parainfluenza virus and human Boca virus[30,31]; that is, "any respiratory virus."

RSV has two strains, A and B, with RSV A associated with more severe disease.[32,33] Reinfection in the same season with the same or different strain is possible.[34] As a sole infecting agent, RSV is associated with more severe bronchiolitis than other single respiratory virus infections.[5] Coinfection of RSV with rhinovirus can produce even more severe disease.[35] RSV is the most common infectious agent in children admitted to the hospital with radiological features consistent with pneumonia (occurring in 28% of children—most commonly those under 5 years of age).[36] In young children who are well immunized, RSV represents the most common cause of lower respiratory tract infection.[37]

Pathology/Pathogenesis

What commences as an upper respiratory tract infection becomes a lower respiratory tract infection over the course of 2 to 5 days. Infants are particularly susceptible as they have small bronchi that are more likely to become blocked by secretions and edema, and a less well-developed ability to respond to and clear viral infection.[38]

Histopathology is naturally limited to the most severe cases who have died, where the bronchioles are edematous and blocked by necrotic epithelium and neutrophils, with some mucus binding this debris together.[39] Airway obstruction is intensified by poor airway clearance associated with loss of cilia function occurring within 24 hours and persisting for up to 3 months after the illness.[40] Destruction of cilia is considered to be caused by virus replication and not mediated by inflammation.[38] RSV is associated with more severe airway pathology than that found in children dying from other respiratory viruses, even in those not mechanically ventilated.[39]

Viral shedding is higher and more prolonged in younger infants and those with more severe disease.[41] Increased disease severity, longer hospital stay and use of intensive care is associated with higher viral load for RSV in nasopharyngeal secretions.[42,43] Severity of disease is associated with both infant risk factors (including lack of adaptive T cell response),[26,44] but also RSV virus specific factors (viral antigen load and direct cytotoxic effects).[45] Determining the relative contribution of both of these to disease severity will be important; if the latter is dominant, antiviral agents provided early in the course of the disease may reduce severity, whereas dominance of the former might need additional immunomodulators.[4]

Biomarkers are now sought to better characterize those at risk of greater disease severity and to indicate recovery. Infants hospitalized with RSV bronchiolitis have increased interleukin (IL)-33 and IL-13 in secretions.[46] Polymorphisms of surfactant protein A are associated with increased risk of intensive care admission.[47] Cysteinyl leukotrienes are increased in infants with RSV bronchiolitis and are still increased 1 month following infection.[48] More severe disease is also associated with increased serum cathelicidin,[49] lactate dehydrogenase, caspase[50] and IL-15.[51] There is some evidence that more severe disease may be associated with an insufficient inflammatory response.[52] The interrelationship of the microbiome in bronchiolitis is also being actively explored.[53]

Clinical Features

Bronchiolitis is diagnosed clinically. Variance in the clinical interpretation of symptoms and physical findings lead to inconsistency in diagnosis, particularly in milder cases and children over 1 year of age.

SYMPTOMS

Typical symptoms are rhinorrhea, proceeding over 2 to 4 days to a characteristic harsh moist cough with pyrexia that is typically below 39°C, although fever above 38.5°C is seen in 50% of infants.[54] Ability to achieve adequate oral feeding

declines as nasal obstruction with secretions develops and work of breathing increases. The time to peak symptoms of 4 days is associated with the peak in viral load,[42,55] varying from infant to infant.

In younger children (particularly <6 weeks of age), apnea may be a presenting sign, sometimes in the absence of other features of bronchiolitis. Apnea may be temporarily improved by nasal suctioning, but it is most likely a direct viral effect in young infants.[56] Apnea is a "red flag" sign in bronchiolitis that warrants a period of review in a supervised clinical setting to ensure that it has resolved.

Patients more likely to require intensive care include preterm infants and those with apnea, low birth weight, or a respiratory rate greater than 70/min.[57,58] Children tend not to relapse during the improving phase of the illness, which should give confidence to clinicians when considering discharge from ED or hospital.[58,59]

PHYSICAL FINDINGS

Physical findings include an increased respiratory rate, chest recession, use of accessory muscles, hyperinflation, wheezing, crackles, and reduced arterial oxygen saturations.[60] Physical findings vary depending on sleep state (and associated changes in tidal volume). Respiratory rate is a key marker of disease severity, with ≥60/min considered severe and ≥70/min critical.[26,61] Oxygen saturation may be improved (at least temporarily) by removal of nasal secretions.[62]

CLINICAL SCORES

Bronchiolitis is a highly variable disease that requires assessment of disease severity by clinicians for decision making, some of which is subjective. Clinical scoring systems have been developed in an attempt to standardize care and minimize variance. Many early scores derived from asthma scores. The most commonly applied scores for bronchiolitis are outlined in Table 24.1. Within this table, the most widely quoted is the Respiratory Distress Assessment Instrument (RDAI)[63] (and the resulting Respiratory Assessment Change Score, RACS). More recent scores were developed to have more detailed validation (Liverpool Infant Bronchiolitis Severity Score–Proxy Reported Outcome Measure [LIBSS PRO][64] and Genetics, Vaccines and Infectious Diseases Paediatrics Research Group [GENVIP][65]) and to improve the ability to identify those at risk of deterioration. The ability of clinical scores to retain precision and reliability, when scoring is performed by larger numbers of health care professionals in the context of multicenter Phase III trials, is of current interest.

DISEASE SEVERITY

Symptoms in bronchiolitis vary across a wide but skewed continuum from mildly increased work of breathing with cough to respiratory failure and death. Often divided into mild, moderate, and severe disease, the perspective on these gradations varies across health care systems. A World Health Organization (WHO) workshop has provided candidate definitions differentiating a diagnosis of RSV lower respiratory tract infection (SpO_2 <95%) from severe (<93%) and very severe RSV disease (SpO_2 <90%, inability to feed orally, or reduced level of consciousness).[66] Infants can display variance in SpO_2 within this range (90% to 95%) over short periods of observation without significant change in clinical status,[58,62,67] which may limit the discriminatory reliability of these definitions. From a secondary care perspective, moderate severity is often considered a need for admission to hospital and severe by need for critical care (positive pressure support). Clinical scores are often designed to identify transition points in the level of care required.[64] The currently available evidence concerning transition points in level of care is poor. Treatment guidance, particularly benefit from use of interventions at the ED/Ward (i.e., SpO_2)[68] and ward/critical care floor interface (i.e., high-flow nasal cannula [HFNC] oxygen and continuous positive airway pressure [CPAP]) is much needed. Guidelines have provided signs and symptoms that should alert clinicians to a child at risk of deterioration and suggested criteria for admission to the hospital.[26] In hospitals, those most likely to deteriorate to the extent of being provided with critical care support are of lower birth weight (<5 lbs, 2.25 kg) and/or have a respiratory rate ≥70/min on day 1 of admission.[57]

IMAGING, LABORATORY FINDINGS

Chest radiography is not required to confirm a diagnosis of bronchiolitis. A chest radiograph often leads to increased diagnostic uncertainty as the features may be similar to those of pneumonia (atelectasis, mucous plugging, and loss of volume) and consequently lead to greater inappropriate use of antibiotics.[69] Chest radiography should be reserved for a child who is atypical, for example, showing persistently focal crackles, a temperature remaining above 39°C despite antipyretics, or respiratory failure requiring critical care support.[26,70]

Laboratory tests do not aid in the clinical diagnosis of bronchiolitis. Serious bacterial infection is unusual and complete blood counts and blood cultures are unhelpful (though recent evidence suggests that although still uncommon, it may be more frequent than previously considered).[65] Dehydration is usually mild and best assessed clinically without electrolyte measurement. Approximately 6% of infants with bronchiolitis can have concurrent urinary tract infection, so urine culture may be of value in persistently febrile infants, particularly those under 3 months of age.[71]

Measurement of arterial/capillary carbon dioxide is commonly performed, but can be restricted to those children with increased respiratory rate and work of breathing despite oxygen supplementation.[72]

Diagnosis and Differential Diagnosis

The clinical interpretation of signs and symptoms is difficult in a condition where age boundaries are loose (and skew to older ages in those with comorbidity) and symptoms vary from patient to patient and time to time. This naturally leads to variation in diagnosis and differential diagnosis. There is a common understanding that a clearer diagnosis is possible in those under 1 year of age and most guidelines reflect this. However, constraining a diagnosis of bronchiolitis to those less than 1 year of age may reduce the ability to identify the whole population of children with bronchiolitis who could benefit from potential interventions. In general, a broader

Table 24.1 Clinical Scores for Bronchiolitis

Score	Tal[a]	Lowell[b]	Wang[c]	Wilson[d]	Jacobs[e]	Liu[f]	Walsh[g]	Marlais[h]	Van Miert[i]	Cebey-Lopez[j]
Name	Tal and later Modified Tal (SpO_2 not cyanosis)	Respiratory Distress Assessment Instrument (RDAI)	No names	Comprehensive Severity Index (pediatric component)	Canadian Acute Respiratory Infection and Flu Scale (CARIFS)	No name	Bronchiolitis Assessment Severity Tool	Bronchiolitis Risk of Admission Scoring System	LIBSS-PRO	GENVIP
General respiratory or bronchiolitis specific	General	General	General	General	General	General	Bronchiolitis	Bronchiolitis	Bronchiolitis	General
Date published	1983	1987	1992	2000	2000	2004	2006	2011	2015	2016
Number of items	4	7 (in 3 domains)	4	27 (in 7 domains)	18 (in 3 domains)	4 (age specific ranges)	4	5	10	7
Subjective/objective	2/2	2/1	3/1	11/14	18/0	3/1	2/2	0/5	3/7	3/4
Scoring	0–3 per item	0 to max 4 per item. Total max = 17	0–3 per item	1–4	0–3 per item	0–3 per item	0 to max 3 + age	0–1	0 to max 8 per item	0–3 (max 20)
Score	Mean score	Sum	Sum	Sum	Sum	Sum	Sum of weighted scores	Sum	Sum	Sum
Interpretation	Relative change	Change in score >4 = improvement, <4 no improvement	Relative change	Relative change	Relative change	Relative change	≤0.654 mild disease, >1.866 severe	≥3 predicted admission	Cut of scores for mild, moderate, and severe	Relative change
For completion by	Health care	Health care	Health care	Health care	Parents	Health care	Health care	Health care	Health care	Health care
Interrater reliability										
Correlation				Length of stay $r^2 = 0.23$				PPV 67% NPV 83%		
Kappa	0.7[k]	Not provided for total score	0.48		0.36–0.52	0.52–0.65	0.68		0.83	0.74

[a]Tal A, Bavilski C, Yohai D, Bearman JE, Gorodischer R, Moses SW. Dexamethasone and salbutamol in the treatment of acute wheezing in infants. *Pediatrics*. 1983;71(1):13-18.
[b]Lowell DI, Lister G, Von Koss H, McCarthy P. Wheezing in infants: the response to epinephrine. *Pediatrics*. 1987;79(6):939-945.
[c]Wang EE, Milner RA, Navas L, Maj H. Observer agreement for respiratory signs and oximetry in infants hospitalized with lower respiratory infections. *Am Rev Respir Dis*. 1992;145(1):106-109.
[d]Wilson DF, Horn SD, Smouth R, Gassaway J, Torres A. Severity assessment in children hospitalized with bronchiolitis using the pediatric component of the comprehensive severity index. *Pediatr Crit Care Med*. 2000;1(2):127-132.
[e]Jacobs B, Young NL, Dick PT, et al. Canadian Acute Respiratory Illness and Flu Scale (CARIFS): development of a valid measure for childhood respiratory infections. *J Clin Epidemiol*. 2000;53(8):793-799.
[f]Liu LL, Gallaher MM, Davis RL, Rutter CM, Lewis TC, Marcuse EK. Use of a respiratory clinical score among different providers. *Pediatr Pulmonol*. 2004;37(3):243-248.
[g]Walsh P, Gonzales A, Satar A, Rothenberg SJ. The interrater reliability of a validated bronchiolitis severity assessment tool. *Pediatr Emerg Care*. 2006;22(5):316-320.
[h]Marlais M, Evans J, Abrahamson E. Clinical predictors of admission in infants with acute bronchiolitis. *Arch Dis Child*. 2011;96(7):648-652.
[i]van Miert C, Abbott J, Verheoff F, Lane S, Carter B, McNamara P. Development and validation of the Liverpool infant bronchiolitis severity score: a research protocol. *J Adv Nurs*. 2014;70(10):2353-2362.
[j]Cebey-Lopez M, Pardo-Seco J, Gomez-Carballa A, et al. Bacteremia in children hospitalized with respiratory syncytial virus infection. *PLoS One*. 2016;11(2):e0146599.
[k]McCallum GB, Morris PS, Wilson CC, et al. Severity scoring systems: are they internally valid, reliable and predictive of oxygen use in children with acute bronchiolitis? *Pediatr Pulmonol*. 2013;48(8):797-803.
LIBSS PRO, Liverpool Infant Bronchiolitis Severity Score–Proxy Reported Outcome Measure.

definition of bronchiolitis is used in North America and Asia that captures a higher percentage of older children with wheezing, where rhinovirus is the dominant infecting agent.[73] Such children may be given a diagnosis of viral induced wheeze in other countries. There is most likely a continuum of viral lower respiratory tract infection across age ranges that moves from current diagnoses of viral bronchiolitis to viral pneumonia and viral-induced wheeze/wheezy bronchitis.[74,75]

The clinical features consistent with a diagnosis of bronchiolitis across different guidelines are presented in Table 24.2. Diagnosis has a typical onset of a viral respiratory tract prodrome proceeding to lower respiratory symptoms over 3 to 4 days. The South African guideline (2010) considers hyperinflation the most reliable clinical sign in bronchiolitis.[76] The UK guideline (2015) provides a more proscriptive definition.[26]

Testing of nasal secretions for virus may help consolidate the clinical diagnosis of bronchiolitis and inform health care logistics. Most commonly used, and with highest precision, are polymerase chain reaction (PCR) diagnostics for a range of respiratory viruses, but point of care (PoC) testing for a more limited range of viruses (most often RSV) is increasingly precise and cost effective.[77] Testing for RSV (as the most common infecting agent in bronchiolitis) is often performed to aid cohorting of patients within hospitals. The increasing recognition that multiple viruses may be identified in those with acute bronchiolitis has called into question the benefit of cohorting based on RSV status.[78] PCR diagnostics may sometimes be considered oversensitive to the detection of virus fragments postinfection, and multiplex PCR results should be interpreted with this understanding.

Differential diagnosis includes bacterial pneumonia or an alternative cause of crackles, wheeze, and increased work of breathing in a young child. Persisting crackles (crepitations) in one lung zone, fixed focal wheeze, persistent pyrexia (>39°C) or persistently increased work of breathing in a child who appears otherwise recovered warrant further evaluation.

Prescient in the mind of most clinicians is that a bacterial pneumonia may be missed. Chest radiographs have similar appearances and are poor discriminators. We can assume that bacterial coinfection risk is low, as the use of antibiotics in bronchiolitis is not associated with faster recovery.[79] Further investigation could be limited to those with the persisting clinical features noted above. In children with more severe disease, there may be a role for antibiotics as bacteria are isolated in 33% to 44% of lavage samples in children with severe bronchiolitis who are intubated and ventilated.[80–82]

Table 24.2 Guideline Recommendations in Bronchiolitis

	Spain (2010)	South Africa (2010)	Canada (2014)	United States (2014)	United Kingdom (2015)	Finland (2016)	Recent Evidence That May Influence Future Recommendations[a]
Age	<24 months	Children	≤2 years	1–23 months	Children (mostly under 1 year)	Children (mostly under 6 months)	
Clinical definition	Not stated	Viral URTI, with poor feeding, low-grade fever, hyperinflation of the chest, wheezing, tachypnea, lower chest wall retractions	Viral URTI, cough or rhinitis followed by some of tachypnea, costal retractions, apnea, wheezing or crackles, nasal flaring, hypoxemia	Rhinitis and cough, followed by tachypnea, wheezing, rales, use of accessory muscles and/or nasal flaring	Coryza followed by persistent cough and tachypnea or chest recession (or both) and wheezing or crackles (or both). Apnea may be presenting symptom in absence of above.	Not stated. Fine crackles on auscultation considered characteristic.	
THERAPIES							
Oxygen supplementation threshold	<92%	<92% (<90% above 1800 m)	<90%	<90%	<92%	"Low"—not defined	Cunningham
Bronchodilator	No	Trial in hypoxic infant	No	No	No	No	
Hypertonic saline	No	Trial in hypoxic infant	?Equivocal	Trial in hospitalized child	No	No	Everard Florin Teunissen Jacobs Wu Silver
Corticosteroids	No	No	No	No	No	No	
Epinephrine	No	No	?Equivocal	No	No	No	
Antibiotics	No	Consider if severe	No	No	No	No	

[a]See "Suggested Reading" section.
URTI, Urinary tract infection.

There are no trials of outcome for antibiotic use in children with bronchiolitis receiving intensive care.

Though uncommon, congenital lesions may masquerade as bronchiolitis, and this should be borne in mind for children with atypical clinical features or those slow to recover. Congenital heart disease may present as bronchiolitis when pulmonary vascular resistance falls increasing left to right shunt. More difficult to differentiate are children with congenital (or less commonly acquired) pulmonary malformations. Fixed focal wheeze may be a sign of tracheomalacia or bronchomalacia, stenosis, or compression from lobar emphysema or a bronchogenic cyst and would warrant a chest radiograph. A slow recovering course with persistent chest signs could be an infected congenital pulmonary malformation (such as a congenital cystic adenomatoid malformation [CCAM] or sequestration). Children with persistent fine crackles, tachypnea, and low (often borderline) oxygen saturation may have an interstitial lung disease, particularly neuroendocrine cell hyperplasia (NEHI) presenting as recurrent "bronchiolitis." Young children with persistent, sometimes focal, crackles postadenovirus (though may also be other respiratory viruses and mycoplasma pneumonia) should be evaluated for postinfectious bronchiolitis obliterans (PIBO); see section 6 of the book.

Management and Treatment

Management of bronchiolitis is supportive, assisting hydration and hypoxemia until improvement. With increased respiratory rate and nasal secretions, oral feeding is challenged, and those with severe disease require assistance with feeding by enteral or parenteral means. The threshold for supporting hydration is typically when an infant's intake is reduced to 50% to 75% of usual volume. The chosen percentage of intake depends on the child's status: an expreterm 10-week-old infant on day 3 of illness may be supported at 75% understanding that they most likely will deteriorate, whereas a robust 8-month-old term infant may be able to tolerate 50% feed volume for a couple of days until disease resolution. Nasogastric feeding is easier to administer than intravenous fluids but has no advantage in recovery from acute disease.[83]

Oxygen may be used to treat hypoxemia. The threshold oxygen saturation at which to use supplemental oxygen varies across guidelines and is typically set between 90% and 94% at sea level. In children admitted to hospital with bronchiolitis, management at a threshold of 90% SpO_2 is safe and as clinically effective as a 94% target.[84] The threshold oxygen saturation for admission to hospital is often 92%, as some data suggest that infants have a higher risk of desaturating further at this oxygen saturation.[85] Oxygen desaturation may however have a disproportionate influence on decisions to admit children to the hospital,[68] and much like hydration status (previously mentioned), the context of the measurement should be considered. Many infants discharged home from ED with bronchiolitis experience desaturation events subsequently that are not associated with clinical deterioration.[67] In hospitals, the use of intermittent oxygen saturation monitoring is much discussed, and though the benefit below 90% SpO_2 is not established, once stable above 90% SpO_2, oxygen saturation monitoring should be stopped.[86] Use of therapies in addition to supplemental oxygen and hydration are poorly supported by current evidence. There is some evidence that infants handled less get better quicker,[87] and the use of additional therapies should be considered with that in mind.

There is widespread variation across hospitals and countries in the management and treatment of bronchiolitis reflecting local custom and individual clinician practice.[88] Reducing variation and associated health care costs is a key aim of bronchiolitis management presented through guidelines. Guidelines for the care of infants with bronchiolitis based on systematic review and published in English are available from the United Kingdom (2015),[89] United States (2014),[90] Canada (2014),[61] Spain (2010),[91] Finland (2016),[92] and South Africa (2010),[76] which has been updated as a critical review 2016.[93] No therapies receive support across all guidelines for use with the exception of supplemental oxygen. Chest physiotherapy does not speed recovery. Antibiotics, though still widely used, are of no benefit in bronchiolitis.[79] In addition, bronchodilators are less likely to be recommended in more recent guidelines, and the theory that they may be of greater benefit in infants more likely to develop asthma has been refuted.[94] Nebulized hypertonic saline has been of benefit in cystic fibrosis and in early trials in bronchiolitis,[95] but larger well-designed trials have not demonstrated a persuasive benefit.[96–100]

Recent years have seen the increasing use of HFNC oxygen in acute bronchiolitis.[101] Though clinical trials have not yet demonstrated important clinical or physiological benefits,[102] large well-designed trials are in progress and are beginning to report.[102a,103] CPAP has some benefit in bronchiolitis, and may prevent deterioration when used early.[104] As with all management in bronchiolitis, the use of HFNC oxygen, CPAP, and intubation varies across sites irrespective of disease severity,[105] and better understanding of the risks and benefits of these interventions is required.[106]

There are no current effective pharmacological treatments for RSV. While ribavirin was previously used as an antiviral treatment for RSV, it is now considered ineffective.[107] Novel treatments for acute infection are in development: antivirals and nebulized immunoglobulin. In this rapidly moving field, it seems probable that a treatment for RSV will become available in the next 5 years.[108] Reduction in viral load has been demonstrated in adult challenge models of RSV treated with the antivirals ALS-8176[109] and GS-5806[110]

Prevention

Prevention of spread of RSV depends on good hygiene, in particular, hand washing, as RSV may survive for up to 6 hours on surfaces contaminated by droplets.[111] Similar precautions are appropriate for other respiratory virus infections associated with bronchiolitis. Many hospitals use PoC testing for RSV to determine cohorting of infants as inpatients.[107] While this is still common, the practice is called into question by the range of coinfection with other respiratory viruses revealed by PCR panel testing; up to 62% of children with viral respiratory tract infection have more than one virus detected.[112]

Prevention of RSV (as the most common cause of bronchiolitis) has been a long-term goal. Early formalin inactivated

vaccines were associated with more severe enhanced RSV disease and deaths, possibly resulting from inadequate T cell priming.[113] Subsequent vaccine development has been cautious in view of this experience.

In the 1990s, RSV intravenous immunoglobulin was developed[114,115] but was rapidly superseded by palivizumab, a monoclonal antibody delivered by monthly intramuscular injection. When administered over the RSV season, it reduces hospital admission in high-risk infants.[116] Palivizumab's monthly injections and limited efficacy have prompted the development of extended life monoclonal antibodies that are undergoing licensing trials in preterm infants.[117] They will hopefully be evaluated in the future for high-risk infants born at term.

RSV vaccine development has gained significant impetus over the last 15 years with a wide range of candidate vaccines in development both for pediatric and maternal use; maternal immunization could provide passive transplacental protection to infants in the first 3 to 6 months of life (http://www.path.org). A Phase III trial of maternal immunization by Novovax is expected to conclude in 2020.

Prognosis

For most children, bronchiolitis is a self-limiting disease, with cough as the most persistent symptom resolving at a median of 12 to 15 days.[84,118] Many children, however, develop recurrent respiratory symptoms. In the first few months following illness, this is considered in part to result from loss of cilia from the airway epithelial surfaces during the acute illness.[40] For those who experience chronic symptoms, the debate continues on whether children with more severe bronchiolitis and recurrent postinfectious wheezing have premorbid susceptibility, with some evidence suggesting poorer preexisting lung function.[119] Recurrent wheeze in the year following bronchiolitis occurs in 62% of those who are RSV positive and 32% of those who are RSV negative.[120] Recurrent postinfectious wheeze is not reduced by montelukast[121] or inhaled corticosteroids,[122,123] but there is good evidence of benefit from Palivizumab,[124] and potentially azithromycin,[125] though the latter requires further study.

In the longer term, there is good evidence that children who have had an admission to the hospital for RSV bronchiolitis are 3 times more likely to have a diagnosis of asthma and lower lung function at age 6 years[23] and a higher incidence of asthma at age 13[126] and 18[127] years. The question remains whether such children are predisposed to bronchiolitis because of premorbid anatomy[119] and the consequent interrelationship between host and virus specific effects on the development of asthma.

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Access the reference list online at ExpertConsult.com.

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