

Bronchiolitis: Systematic Review with 3 Decades of Experience in Resource-limited Setting

Suraj Gupte*

Professor and Head, Postgraduate Department of Paediatrics, Mamata Medical College and Hospitals, Khammam, Telangana, India

***Corresponding Author:** Suraj Gupte, Professor and Head, Postgraduate Department of Paediatrics, Mamata Medical College and Hospitals, Khammam, Telangana, India.

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Abstract

Bronchiolitis is a common paediatric problem most frequently affecting 7 to 12-month-old infants. One-third of cases may present as an emergency responsible for hospital admissions in infants under the age of one year. Respiratory syncytial virus (RSV) is the causative pathogen in a vast majority of the cases.

Respiratory distress, tachypnea, wheezing, feeding difficulty and chest retractions preceded by an upper respiratory infection are the most common clinical features.

Diagnosis is by and large clinical. Chest x ray and total leukocyte count do not aid much in diagnosis. Even, oxygen saturation may be normal in most of the cases. Confirmation of diagnosis is possible by antigen testing of nasal or nasopharyngeal aspirates, viral immunofluorescence or PCR.

Mainstay of treatment revolves around humidified oxygen, judiciously administered fluids and maintenance of nutrition. Whereas bronchodilators are of limited value, steroids hardly have a role in its therapy. Antiviral drugs (ribavirin) may occasionally be employed in severe cases, especially in the presence of an underlying condition such as congenital heart disease, cystic fibrosis, asthma, etc. Hand and environmental hygiene, humanized monoclonal antibodies and vitamin D are believed to have a prophylactic role in vulnerable subjects.

Keywords: Chest Retractions; Epinephrine; Humanized Monoclonal Antibodies; Humidified Oxygen; Nebulisation; Palivizumab; Ribavirin; Respiratory Syncytial Virus; Severe Bronchiolitis; Immunofluorescence; Vitamin D; Wheezing

Introduction

Amongst the lower respiratory tract (LRT) infectious diseases in infants and young children, severe bronchiolitis is by and large the most common emergency during winter in particular [1-4].

Severe bronchiolitis is characterized by inflammation of bronchioles (often along with bronchi), resulting in respiratory distress, usually in infants with significant morbidity and mortality [2]. Coexistence of such conditions as cardiopulmonary disease (congenital heart diseases, chronic lung disease such as asthma or cystic fibrosis), or immunodeficiency is accompanied by enhanced risk of not only severe and prolonged illness but also complications which, if not timely treated, may prove fatal [1,3].

Epidemiological Considerations

Bronchiolitis, occurring in both epidemic and sporadic forms, develops following spread of infection by direct contact with respiratory secretions.

Globally, most cases of bronchiolitis occur during winter followed by autumn and spring. In our experience in India, cases continue to be seen in all remaining seasons too though less frequently [1]. In 2016, in our experience in a South Indian tertiary care hospital, 80% of cases of severe bronchiolitis were seen in October-January; rest of the 20% were spread over the remaining months. Similar was our earlier experience in north India [4].

Bronchiolitis occurs primarily in the first 2 years of life with peak incidence between 6 - 12 months of age.

Etiologic Considerations

Most often, bronchiolitis is the result of viral infection. The viruses incriminated include

- Respiratory syncytial virus (RSV)
- Adenoviruses
- Influenza viruses (A and B)
- Parainfluenza viruses
- Herpesvirus
- Enteroviruses
- Human metapneumovirus.

Such pathogens as *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Streptococcus haemolyticus*, *Haemophilus influenzae* and *Haemophilus pertussis* may also cause bronchiolitis or bronchiolitis-like illness.

Even allergy has been incriminated in its etiology. Convincing evidence in support of this observation is yet to be available.

Pathophysiology [1]

Bronchiolitis is characterised by:

- Acute inflammation, oedema, and necrosis of epithelial cells lining the bronchioles (to some extent, bronchi as well)
- Increased mucus production,
- Narrowing of the small airway (bronchi) lumen.

All of these factors contribute to obstruction of the small airways.

On an average, duration of illness is approximately 2 weeks. However, nearly 20% of patients may have symptoms lasting longer than 3 weeks.

Usually, infection of the smaller airways produces increased mucus secretion, cell death, and sloughing, followed by a peribronchiolar lymphocytic infiltrate and submucosal oedema. The combination of debris and oedema produces critical narrowing and obstruction of smaller airways.

Ventilation/perfusion mismatching, resulting in hypoxia, is the outcome of reduced ventilation of a portion of the lung. During the expiratory phase, further dynamic narrowing of the airways produces disproportionate airflow decrease and resultant air trapping. Work of breathing is increased due to increased end-expiratory lung volume and decreased lung compliance.

After 3 - 4 days, recovery of pulmonary epithelial cells follows. However, cilia take about 2 weeks to regenerate. Macrophages clear the debris.

Clinical Manifestations

A classical patient is an infant, aged 6 - 12 months, who begins with an upper respiratory infection in the form of rhinorrhoea, mild cough and sneezing. Later, the infant develops breathlessness with rapid, shallow breathing, feeding difficulty and prostration. Fever may be mild to moderate.

If breathlessness is marked, air hunger, flaring of alae nasi, chest retractions and cyanosis follow.

Clinical manifestations may worsen, ending up with dehydration, electrolyte imbalance and respiratory acidosis.

Chest signs include retractions (intercostals, subcostal and suprasternal), hyper-resonant percussion note from emphysema, diminished breath sounds and widespread wheeze with or without some crackles.

Differential Diagnosis

Bronchiolitis needs to be differentiated from certain clinical conditions as listed in box 1.

- Asthma: frequent exacerbations
- Bronchopneumonia: coarse crackles are the dominant finding. Wheeze, if present, is mild.
- Foreign body in the airway: history of inhalation, localized wheeze, signs of collapse/emphysema
- Congestive cardiac failure: fine crackles with other signs of heart failure.
- Gastroesophageal reflux: breathing problem over and above existing digestive symptoms; acute von recurrent problem; response to anti-reflux therapy
- Congenital anomalies, such as a vascular ring or congenital heart disease

Box 1: Differential diagnosis of bronchiolitis.

Diagnosis

A good history and physical examination (Box 2) are crucial to the diagnosis which, in most cases, is a sheer clinical exercise.

History

- History and physical examination form the primary basis for the diagnosis of bronchiolitis.
- Early symptoms are those of a viral upper respiratory tract infection (URTI), including mild rhinorrhoea, cough, and sometimes low-grade fever.
- Older children and many infants do not progress beyond this stage of URTI.
- For the 40% of infants and young children who progress to lower respiratory tract involvement, paroxysmal cough and dyspnoea develop subsequently.
- Other common symptoms include the following [5,6]:
- Fever,
- Increased work of breathing,
- Wheezing,
- Cyanosis,
- Grunting,
- Noisy breathing,
- Vomiting, especially post-tussive,
- Irritability,
- Poor feeding or anorexia.

Physical Examination

Most patients with bronchiolitis have the following signs [5,6]:

- Tachypnea, often at rates over 50 - 60 breaths per minute (most common physical sign),
- Tachycardia
- Fever (usually mild),
- Cyanosis,
- Otitis media,
- Nasal flaring,
- Mild conjunctivitis or pharyngitis,
- Intercostal retractions,
- Diffuse expiratory wheezing,
- Inspiratory crackles,
- Apnoea, especially in infants younger than 6 weeks,
- Palpable liver and spleen from visceroptosis secondary to hyperinflation of the lungs and consequent depression of the diaphragm.

Box 2: Clinical workup in suspected bronchiolitis.

Clinical Scoring System for Severity

Of quite a few scoring systems, an important clinical scoring system is the Respiratory Distress Assessment Instrument (Table 1). It was developed in 1987 by Lowell, *et al.* [7] It is known for good inter-observer reliability [8].

	Points					Maximum points
	0	1	2	3	4	
Wheezing						
Expiration	None	End	½	¾	All	4
Inspiration	None	Part	All			2
Location	None	Segmental: > 2 of 4 lung fields	Diffuse: > 3 of 4 lung fields			2
Retractions						
Supraclavicular	None	Mild	Moderate	Marked		3
Intercostal	None	Mild	Moderate	Marked		3
Subcostal	None	Mild	Moderate	Marked		3

Table 1: Respiratory Distress Assessment Instrument (RDAI).

Note: Score 7 - 15: Mild; 16 - 30: Moderate; > 30: Severe

It needs to be re-emphasised that the diagnosis of bronchiolitis is usually a clinical one. Investigations are not generally needed to confirm it. A chest film showing hyperinflated lungs with patches of atelectasis is somewhat helpful.

Criteria for Hospitalization

Vital signs and scoring systems for respiratory distress are of limited help in determining as to which infant with mild disease is likely to subsequently develop a severe illness and hence hospitalisation. Hardly any single clinical criteria for hospital admission (including oxygen saturation, respiratory rate, apparent respiratory distress, and day of illness) is good enough.

In our opinion, attending paediatrician’s clinical impression of the infant’s appearance is quite a dependable predictor of severe illness.

All in all, oxygen saturation (SpO₂) < 95% is, by and large, the most objective predictor of severity.

The admission criteria in bronchitis are presented in box 3 [1].

<p>Admission Criteria</p> <ul style="list-style-type: none"> • Apnea • Requiring oxygen to maintain SpO₂ > 92% • Requiring support with hydration/nutrition • Heart failure
<p>Lower Threshold for Admission</p> <ul style="list-style-type: none"> • Pre-existing lung disease, congenital heart disease, neuromuscular weakness, • Immuno-incompetence • Age < 6 weeks (corrected) • Prematurity • Family anxiety • Re-attendance

Box 3: Criteria for hospitalisation.

Investigations

Chest X-ray: CXR may reveal

- Hyperinflation/emphysema
- Patchy infiltrate
- Atelectasis
- Reticular nodular pattern
- Low-lying diaphragm
- Widening of intercostal spaces.

ABG: When saturation on pulse-oximetry is < 92%.

Virologic tests: Rapid antigen detection tests are the most commonly used techniques in the Western countries.

Therapeutic Approach in Severe Bronchiolitis

Though severe bronchiolitis is an emergency, management is mostly symptomatic and supportive [9-12].

Measures include

- Humidified oxygen inhalation through face mask or head box,
- Atmosphere well saturated with water vapors,
- Mild sedation,
- Postural drainage and
- IV fluids to combat dehydration.

Humidified oxygen is indicated when oxygen saturation is < 94% as such or in combination with clinically significant respiratory distress.

Bronchodilators

Bronchodilators are better avoided. Rather than doing any good, they may increase the cardiac output and restlessness [1].

If opted for, preferred drug is salbutamol or racemic or levo epinephrine by nebulization.

Salbutamol (albuterol) is a selective beta-2 agonists that acts by relaxing the pulmonary smooth muscle and, thereby, decreasing airway resistance. Other purative mechanisms are suppression of inflammatory mediators from mast cells, decreased microvascular permeability, and enhanced mucociliary function. Since infants have a paucity of smooth muscle, there is less likely to be benefit from albuterol inhalation.

Understandably, the paucity of smooth muscle in part may account for the very modest benefit noted in patients with bronchiolitis. The peak effect of albuterol is noted within 15 minutes with duration of effect up to 3 or 4 hours. The usual dose for young patients with bronchiolitis is 0.02 ml/kg (0.1 mg/kg) to 0.03 ml/kg (0.15 mg/kg) with a minimum of 0.5 ml or a single dose of 0.3 ml/kg (1.5 mg/kg). Hypoxemia has been noticed after albuterol administration, presumably because of the worsening of the ventilation perfusion mismatch. It tends to be short in duration and not of significant clinical concern.

Hypertonic Saline Nebulisation

It is a recommended therapy [13-15]. We find it quite effective in improving airway hygiene and thus mucus plugging that contributes to breathing problem. In fact, it is routine therapy in bronchiolitis in our setup.

A Cochrane review [16] concludes that nebulised 3% saline may significantly reduce the length of hospital stay among infants hospitalised with non-severe acute viral bronchiolitis and improves the clinical severity score in both outpatient and inpatient subjects.

Nebulised Epinephrine

A Cochrane review [17] highlights the superiority of epinephrine compared to placebo for short-term outcomes in bronchiolitis outpatients, especially in the first 24 hours of care.

Steroids

Though some clinicians believe that early treatment with steroids might shorten the duration of illness, this is not well-founded. In fact, steroids are likely to do more harm than benefit to the infant with severe bronchiolitis [1,4]. So far, only a solitary study suggests the benefits of epinephrine plus steroid combination for outpatients with bronchiolitis. Obviously, more studies are needed to confirm or refute this observation.

According to a Cochrane review [18], current evidence does not support a clinically relevant effect of systemic or inhaled glucocorticoids on admissions or length of hospitalization. Combined dexamethasone and epinephrine may reduce outpatient admissions. However, results are exploratory and safety data limited. Future research work needs to evaluate the efficacy, adverse drug reactions and applicability of such a therapy.

Antiviral therapy

Ribavirin therapy, though usually not required, may be considered in severe bronchiolitis in underlying conditions listed in box 4 [19,20]:

Definitive <ul style="list-style-type: none">• Severely immunocompromised patients who develop laboratory confirmed RSV-associated bronchiolitis, such as children undergoing bone marrow transplantation• Patients on mechanical ventilation.
Relative <ul style="list-style-type: none">• Cystic fibrosis• Congenital heart disease• Asthma
Dose is 10 mg/kg/day, continuous aerosolization, 10 - 18 hours daily for 3 - 7 days.

Box 4: Indications for ribavirin therapy.

Antibiotic therapy

It may be given only in the presumption of a causative or superimposed bacterial infection.

The key take-home message is not to routinely prescribe bronchodilators, antibiotics or steroids in bronchiolitis.

Prognosis and outcome

- The case fatality rate for bronchiolitis is highest among young infants between 1 and 3 months of age.
- Former premature infants with birth weights less than 1500g have a bronchiolitis mortality rate of 30 per 100,000 live births.

The presence of underlying medical conditions, such as congenital heart disease or chronic lung disease, is another important predictor of poor outcome. In these high-risk children, the case fatality rate may be as high as 5%.

Complications

Box 5 lists the various complications of severe bronchiolitis [1].

<p>Short-term</p> <ul style="list-style-type: none"> • Rapidly progressive exhaustion, anoxia and death • Dehydration, electrolyte imbalance and acid-base imbalance, especially respiratory acidosis • CCF • Bacterial superinfection: Bronchopneumonia, acute otitis meda (AOM)
<p>Long-term</p> <ul style="list-style-type: none"> • Bronchiolitis obliterans: Obliteration of bronchioles by nodular masses consisting of granulation and fibrotic tissue leads to obstructive lung disease. • Hyperlucent lung syndrome (Swyer-James syndrome, Macleod syndrome)
<p>Obstructive lung disease from bronchiolitis obliterans may also be seen in such inflammatory conditions as juvenile idiopathic arthritis (JIA), (systemic lupus erythematosus (SLE), scleroderma, Stevens Johnson syndrome (SJS), and inhalation of toxic fumes (NO₂, NH₃) and following lung and bone marrow transplantation. Hyperlucent lung syndrome is characterised by a diminished perfusion and vascular marking.</p>

Box 5: *Complications of bronchiolitis.*

Prevention

Prevention of bronchiolitis includes [21,22]

1. Environmental prophylaxis to decrease transmission of respiratory infections and, specifically for RSV-caused bronchiolitis.
 - Hand hygiene
 - Equipment, including stethoscope, hygiene
 - Using masks by attendants/visitors with respiratory infection
 - Avoiding exposure to second hand cigarette smoke
2. Pharmacological prophylaxis using
 - Humanized monoclonal antibodies (palivizumab) during the epidemic season in infants and toddlers-at-risk (Box 6).

- Children younger than 24 months of age with chronic lung disease (CLD) of prematurity who have required medical therapy for CLD within 6 months before the start of the RSV season.
- Infants born at 28 weeks of gestation or earlier who are younger than 12 months of age at the start of the RSV season.
- Infants born at 29 to 32 weeks of gestation who are younger than 6 months of age at the start of the RSV season.
- Infants born between 32 and 35 weeks of gestation, who are younger than 6 months of age at the start of the RSV season and have 2 or more of the following risk factors: child care attendance, school-aged siblings, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease.
- Children who are 24 months of age or younger with hemodynamically significant cyanotic and acyanotic congenital heart disease. This includes infants who are receiving medication to control congestive heart failure, infants with moderate to severe pulmonary hypertension, and infants with cyanotic heart disease.

Box 6: *Indications for administering palivizumab in bronchiolitis.*

- Vitamin D: vitamin D supplementation for pregnant women and for infants might be a useful strategy in preventing viral respiratory infections causing bronchiolitis. Currently recommended doses are 400 IU/day for infants (< one year) and 600 IU/day for older children.

Conclusions

Bronchitis, usually a viral infection, is a common problem of infants and toddlers. Severe bronchitis, a common emergency in infants, needs prompt hospitalization. The mainstay of treatment is humidified oxygen along with fluid therapy and adequate nutrition, prevention of superimposed infection (such as pneumonia), and heart failure. Use of bronchodilators must be restricted to very ill subjects not responding to usual line of therapy. Steroids need to be withheld. Antiviral drug, ribavirin, is strongly recommended in infants with certain underlying conditions such as cystic fibrosis and immunodeficiency. Environmental prophylaxis may be helpful. Pharmacological prophylaxis is important in special circumstances such as prematurity.

Take Home Messages

- Bronchiolitis, in its severe form, is a common pediatric emergency.
- RSV is the causative pathogen in a vast majority of the cases.
- Manifestations include upper respiratory infection followed by respiratory distress, tachypnea, wheezing, feeding difficulty and chest retractions.
- Diagnosis is by and large clinical. Chest x ray does not aid much in diagnosis. Even, oxygen saturation may be normal in most of the cases.
- Confirmation of diagnosis is possible by antigen testing of nasal or nasopharyngeal aspirates, viral immunofluorescence or PCR.
- Humidified oxygen and IV fluids remain the mainstay of treatment.
- Though bronchodilators may occasionally be employed in severe cases, steroids offer no benefit.

- Antiviral therapy (ribavirin) is reserved for a small proportion of cases.
- Prophylaxis is environmental as well as pharmacological.
- In uncomplicated cases, prognosis is excellent.

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