Review Article

Acute Bronchiolitis: A Review

Anand Bhutada *, Satish Deopujari**, Yusuf Parvez***
Pediatric & Neonatal Intensivist *, Senior Consultant Pediatrician **, Pediatric Intensivist***, Central India's Child
Hospital & Research Centre, Dhanoti, Nagpur; Specialists Pediatrics, Dubai Hospital, Dubai
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ABSTRACT

Acute bronchiolitis is the most common lower respiratory tract infection (LRTI) in infants and children less than two years of age. It is broadly defined as a clinical syndrome characterized by upper respiratory symptoms followed by lower respiratory infection and inflammation, resulting in wheeze and crackles. Supportive care with focus on oxygenation and hydration remains the mainstay of therapy. Several recent evidence-based reviews reveal that bronchodilators or corticosteroids should not be routinely used in bronchiolitis. This review presents the current status of recent therapies such as nebulized hypertonic saline, heliox, continuous positive airway pressure (CPAP), montelukast, surfactant, and inhaled furosemide, etc.

Key words- Acute bronchiolitis, hypertonic saline, heliox, CPAP

Introduction

Bronchiolitis is the most common cause of hospitalization due to acute lower respiratory tract infection in infants. A substantial proportion of children will experience at least one episode with bronchiolitis, and as much as 2-3% of all children will be hospitalized with bronchiolitis during their first year of life. There is a trend towards increasing incidence of bronchiolitis in recent years. Bronchiolitis is generally seasonal appearing most commonly as epidemics during winter. In India, outbreaks occur from September to March.\(^1\)\(^3\) Bronchiolitis is a disease with high morbidity, but low mortality. Death from respiratory failure in bronchiolitis is rare and range from 2.9 (UK) to 5.3 (USA) deaths per 100 000 children below 12 months of age. In UK mortality rate for bronchiolitis in children below 12 months has declined from 21.5 to 1.8 per 100000 children from 1979 to 2000 reflecting improvement in pediatric intensive care.\(^4\)\(^5\) However, considerably higher mortality rates have been observed for children with cardiopulmonary abnormalities and in immunosuppressed patients.

Risk factors for bronchiolitis are male gender, prematurity, young age, being born in relation to the RSV season, preexisting disease such as bronchodylpasia, underlying chronic lung disease, neuromuscular disease, congenital heart disease, exposure to environmental tobacco smoke, high parity, young maternal age, short duration/no breast feeding, maternal asthma and poor socioeconomic status.\(^6\)\(^8\) These are also risk factors for more severe form of bronchiolitis. Some specific genetic polymorphisms are also known to be risk factors for more severe disease.\(^9\)

Etiology

Bronchiolitis is caused by various viruses. Respiratory syncitial virus (RSV) is the most common (60-70% in less than 1 year) followed by Rhinovirus (14-30%), human bocavirus (14-15%), human metapneumovirus (3-12%), entero-, adeno-, corona and influenza viruses (1-8%). Dual infections are reported in 20-30% of children.\(^6\)\(^10\)\(^12\)

Pathology

Pathologic changes in lungs include detachment and necrosis of epithelium, airway wall edema, infiltration of airway wall and of the interstitium with leucocytes (predominantly macrophages and lymphocytes), and
plugging of airway with mucus and cellular debris. The complete and partial plugging of airways leads to localized atelectasis and overdistension respectively. There is no evidence of smooth muscle hypertrophy in bronchiolitis.13, 14

**Immunology**
Passively acquired maternal immunoglobulins protect newborn from RSV infection during first two months of life. The immunoglobulin levels gradually decrease, leaving most infants unprotected against RSV. Epithelial cells and alveolar macrophages activate cellular immunity by releasing multiple chemical substances including interleukins (IL1,6,8), TNF alpha, MIP 1alpha, RANTES. Children are more likely to wheeze or develop asthma, if RSV infection induces peripheral blood eosinophilia.15

**Clinical Features**
Children with bronchiolitis typically present with an acute viral upper respiratory prodrome comprising of rhinorrhea, cough, and on occasion, a low grade fever. Within 1-2 days of these prodromal symptoms, the cough worsens and child may also develop rapid respiration, chest retractions, and wheezing. The infant may show irritability, poor feeding, and vomiting. Though, in majority of the cases, the disease remains mild and recovery starts in 3-5 days, some of these children may continue to worsen. On examination, most children have tachycardia and tachypnea. Pulse oximetry helps us in deciding about the need for supplemental oxygen. The chest may appear hyper-expanded and may be hyper resonant to percussion. Wheezes and fine crackles may be heard throughout the lungs. Severe cases may have grunting, marked retractions, cyanosis, impaired perfusion and apnea. Examination should include assessment for hydration status (respiratory distress often prevents adequate oral fluid intake and causes dehydration) and co morbidities (chronic lung disease, congenital heart disease, immunosuppressed states).14, 16

<table>
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<tr>
<th>Table 1: Bronchiolitis scoring system</th>
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<td><strong>RR</strong></td>
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<tr>
<td>Normal (&lt;40)</td>
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<tr>
<td>Mild (40-50)</td>
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<tr>
<td>Moderate (50-60)</td>
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<td>Severe (&gt;60)</td>
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<td><strong>Color O2 sat in RA</strong></td>
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<tr>
<td>Normal (&gt;97%)</td>
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<td>Mild (92-96%)</td>
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<tr>
<td>Moderate (90-93%)</td>
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<tr>
<td>Severe (&lt;90%)</td>
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<tr>
<td><strong>Retractions/Work of breathing</strong></td>
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<tr>
<td>None</td>
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<tr>
<td>Subcostal</td>
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<tr>
<td>Intercostals &amp; subcostal when quite</td>
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<tr>
<td>Supraclavicular</td>
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<td><strong>Air entry</strong></td>
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<td>Clear</td>
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<td>Good air entry</td>
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<td>Fair air entry</td>
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<td>Poor air entry</td>
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<tr>
<td><strong>Level of consciousness</strong></td>
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<tr>
<td>Alert</td>
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<tr>
<td>Mild irritability</td>
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<tr>
<td>Restless when disturbed</td>
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<td>Lethargic/ hard to arouse</td>
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**Differential Diagnosis**
Bronchiolitis is so common over the winter months that it can be easy to forget that there are other diagnostic possibilities of respiratory failure in infants. The differential diagnosis includes bronchopneumonia, foreign body, gastroesophageal reflux, congenital heart diseases (Total anomalous pulmonary venous connection), cystic fibrosis, immunodeficiency etc.

| Table 2: Predictors of severe bronchiolitis |

**A. Host Related Risk Factors**
- Prematurity
- Low birth weight
- Age less than 6 to 12 weeks
- Chronic pulmonary disease
- Hemodynamically significant congenital heart disease (e.g., moderate to severe pulmonary hypertension, cyanotic heart disease, or congenital heart disease that requires medication to control heart failure)
- Immunodeficiency

**B. Environmental Risk Factors**
- Having older siblings
- Passive smoke
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• Household crowding
• Child care attendance

C. Clinical Predictors
• Toxic or ill appearance
• Oxygen saturation <95 percent by pulse oximetry while breathing room air
• Respiratory rate ≥70 breaths per minute
• Moderate/Severe chest retractions
• Atelectasis on chest radiograph

Investigations
The diagnosis of bronchiolitis and the assessment of disease severity should be based on history and physical examination. Chest X-ray is not a routine, but when indicated usually reveals hyperinflation, peribronchial thickening and patchy atelectasis. The indications for chest X-ray are when the diagnosis is in doubt, co-morbidity like chronic lung disease or heart disease is suspected, or if the child is severely ill. Similarly, routine laboratory tests are not required. Arterial blood gas may be required in few kids at risk for respiratory failure for CO2 monitoring. Measurement of lactate dehydrogenase (LDH) concentration in the nasal-wash fluid has been proposed as an objective indicator of bronchiolitis severity; increased values (suggestive of a robust antiviral response) have been shown to be associated with decreased risk of hospitalization. Virological studies may not help in treatment or outcome as most viruses present similarly. But positive result can avoid unnecessary antibiotic use in hospital setting. The available tools for etiologic diagnosis include Antigen detection, Immunofluorescence, Polymerase Chain Reaction (PCR), and culture of respiratory secretions obtained by nasal wash or nasal aspirate.

Therapy
Acute bronchiolitis is mostly a mild and self-limiting disease which can be managed on outpatient basis with supportive care, adequate feeding and parental education. Clinician should carefully assess ability of child to accept orally and small frequent feeds should be encouraged. Orogastic or nasogastric tube feeding is an alternative to oral feeds. IV fluids should be given to those with severe illness. A close watch is warranted as these kids are prone for Syndrome of inappropriate anti-diuretic hormone. Nasal block can be relieved by frequent instillation of saline drops in nostrils and gentle suctioning. A prone position may improve oxygenation and is suggested for infants if they are carefully observed. Humidified oxygen should be administered to hypoxemic infants by any technique familiar to the nursing personnel (nasal cannula, face mask, or head box). Pulse oximetry is the most commonly used tool to decide about oxygen supplementation. Supplemental oxygen is indicated if SpO2 falls persistently below 90% in previously healthy infants. Oxygen may be discontinued if SpO2 is at or above 90% and the infant is feeding well and has minimal respiratory distress.

In severe bronchiolitis early intervention in the form of CPAP has been used to prevent mechanical ventilation. CPAP helps in recruitment of collapsed alveoli by opening terminal bronchioles. Airway resistance in terminal airways is reduced with CPAP and also there is decreased air trapping, hyperinflation and work of breathing. However, routine use of CPAP in bronchiolitis requires further studies.

In a prospective cohort study done in children admitted with RSV LRTI, approximately 9% of patients required mechanical ventilation. Indications for intubation and mechanical ventilation are worsening respiratory distress (hypoxemia despite oxygen supplementation), listlessness, poor perfusion, apnea, bradycardia, or hypercarbia.

Inhaled Saline
Inhaled normal saline (0.9%) is commonly used for children with bronchiolitis to increase clearing of mucous. Inhaled hypertonic saline (3%) has shown to increase mucociliary clearance possibly through induction of an osmotic flow of water to the mucus layer and by breaking ionic bonds within the mucus gel. Recent metaanalyses including more than 1000 infants with mild to moderate bronchiolitis...
concluded that the use of hypertonic saline (3-5%) may reduce the length of hospital stay and the rate of hospitalization. However, due to the possible side effect of bronchospasm, all but few patients received a combination with a bronchodilator. A Cochrane review of seven trials involving 581 infants (282 inpatients, 65 outpatients and 234 emergency department patients) with acute bronchiolitis found that nebulisation with 3% saline results in a significantly shorter length of hospital stay as well as a lower clinical score as compared to nebulisation with 0.9% saline. A recent randomized controlled trial reported that high volume normal saline was as effective as 3% saline in children with mild bronchiolitis. Its routine use cannot be recommended till one gets an answer regarding its optimal volume, concentration of saline, frequency of administration and effective device.

**Bronchodilators**

Routine use of inhaled bronchodilators in management of bronchiolitis is questionable. In a meta-analysis of 28 trials (1912 participants) comparing bronchodilators other than epinephrine (included salbutamol, terbutaline, ipratropium) with placebo, there were no significant differences in improvement in oxygenation, hospitalization rate, or duration of hospitalization. A modest improvement in clinical scores was noted in the treated outpatients. Another meta-analysis of 19 trials (2256 participants) compared nebulized epinephrine with placebo or other bronchodilators. Epinephrine versus placebo among outpatients showed a significant reduction in admissions at Day 1 but not at Day 7 postemergency department visit. Epinephrine versus salbutamol showed no differences among outpatients for admissions at Day 1 or 7. Although epinephrine was associated with decreased length of stay compared with salbutamol, epinephrine did not decrease length of stay when compared with placebo.

It is difficult to distinguish bronchiolitis from viral infection associated wheezing or asthma. In the latter condition, broncho-dilators may improve clinical outcome. Therefore, we consider a trial of bronchodilator with careful monitoring. Choice of bronchodilator may be based on personal or family history of atopy or asthma; if present, salbutamol inhalation may be given. In absence of it, a trial of epinephrine inhalation may be given. Further doses of either medication may be continued only on documentation of improvement. There is no role of oral bronchodilators.

**Steroids**

There is no evidence for use of inhaled corticosteroids (ICS) to prevent or reduce postbronchiolitis wheezing after RSV bronchiolitis. A systematic review of 5 studies involving 374 infants did not demonstrate an effect of ICS, given during the acute phase of bronchiolitis, in the prevention of recurrent wheezing following bronchiolitis. An additional RCT involving 243 infants with RSV-related LRTI did not find any effect of inhaled corticosteroids on recurrent wheeze.

A meta-analysis evaluating the use of systemic glucocorticoids (oral, intramuscular, or intravenous) and inhaled glucocorticoids for acute bronchiolitis in children (0 to 24 months of age) included 17 trials with 2596 patients. In pooled analyses, no significant differences were found in hospital admission rate, length of stay, clinical score after 12 hours, or hospital readmission rate. Another meta-analysis (of 3 studies) studied the role of systemic steroids in critically ill children with bronchiolitis. It was found that systemic corticosteroid showed no overall effect on duration of mechanical ventilation. Hence, it is recommended not to use glucocorticoids in healthy infants and young children with a first episode of bronchiolitis.

In a multicentre trial, there was a reduction in hospitalization rates in the group that received dexamethasone and 2 doses of epinephrine by nebulizer as compared with those who were treated with placebo (17.1% vs 26.4%). Number needed to prevent one admission was 1. This study suggests a possible synergy between epinephrine and steroids but need further evaluation to include in any guidelines.

**Antibiotics**

Routine use of antibiotics is not recommended in
Acute bronchiolitis as it will increase the cost of treatment, and lead to adverse reactions as well as development of bacterial resistance. Its use should be restricted to specific population with concurrent bacterial infection \(^{16, 40}\). Clinical setting in presence of consolidation (not just atelectasis or infiltrates) on X ray may indicate bacterial infection in acute bronchiolitis.

**Antivirals**

A systematic review of 10 RCTs (320 participants) reported no improvement in clinical outcome of acute bronchiolitis after ribavirin use \(^{16}\). Ribavirin may be considered in high risk infants (immunocompromised and/or hemodynamically significant cardiopulmonary disease) and in infants requiring mechanical ventilation \(^{16, 38}\). Role of fusion inhibitors (TMC353121, CL387626, RFI-641, JNJ-2408068 etc) \(^{41, 42}\) and leflunomide (immunosuppressant with antiviral activity against RSV) is under trial \(^{43}\).

**Inhaled Furosemide**

Furosemide inhalation in acute bronchiolitis may improve outcome by acting on airway smooth muscle, airway vessels, electrolytes and fluid transport across respiratory mucosa, and reducing airway inflammation. One RCT (32 participants) studied the effect of inhaled furosemide in hospitalized infants with bronchiolitis, and recorded no significant clinical effects in these infants \(^{44}\). Presently there is no evidence for use of inhaled furosemide in the management of bronchiolitis.

**Leukotriene Receptor Antagonists (Montelukast)**

Montelukast is currently not recommended for treatment of bronchiolitis or for prevention of airway reactivity after bronchiolitis as most RCTs had conflicting results \(^{45-48}\).

**Heliox**

Heliox (mixture of helium and oxygen) may reduce work of breathing and improve oxygenation in respiratory illness with moderate to severe airway obstruction including acute bronchiolitis by decreasing airway turbulence. A meta-analysis of four clinical trials (84 participants), using heliox demonstrated improved respiratory distress scores in first hour in children with moderate to severe acute bronchiolitis. However, heliox inhalation did not affect need for intubation and mechanical ventilation and length of stay in pediatric intensive care unit \(^{49}\). Present heterogeneity of various available studies suggests a need to evaluate its role further.

**Surfactant**

A meta-analysis (included three RCTs with total 79 participants) evaluated the effect of exogenous surfactant in infants and children with bronchiolitis requiring mechanical ventilation. The duration of mechanical ventilation and duration of ICU stay were significantly lower in the surfactant group compared to the control group. Use of surfactant had favorable effects on oxygenation and CO2 elimination. No adverse effects and no complications were observed \(^{50}\). Current evidence suggests that surfactant therapy may have potential use in acute severe bronchiolitis requiring mechanical ventilation.

**Prevention**

It is important to avoid nosocomial spread of RSV and other respiratory viruses from children with bronchiolitis. RSV can survive up to seven hours on surfaces and is transmitted directly or indirectly by touch. Air sampling in subjects infected with RSV has detected RSV RNA up to 700 cm from head of the patient’s bed \(^{51, 52}\). General measures like hand decontamination and barrier nursing are important to prevent nosocomial infections \(^{16, 51}\).

Passive immunophylaxis using polyclonal or monoclonal antibodies to high risk infants before RSV season has been documented to reduce admission rates in these infants with acute bronchiolitis. The potential disadvantages associated with polyclonal antibodies include need for intravenous access; risk of transmission of blood-borne infections, possible interference with antibody response to routine immunization specifically live vaccines \(^{53, 54}\). Palivizumab is a humanized mouse IgG1 monoclonal
antibody directed against site A and F glycoprotein of RSV. Palivizumab blocks the fusion of the virus to the host epithelial cells. It reduces RSV infection associated hospitalization in high risk infants but does not reduce mortality rates.\(^6\) Present recommendations for use of palivizumab\(^6\) are

1. 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.
2. Infants born at 28 weeks of gestation or earlier who are younger than 12 months of age at the start of the RSV season.
3. Infants born at 29 to 32 weeks of gestation who are younger than 6 months of age at the start of the RSV season.
4. 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.

Palivizumab is administered intramuscularly at a dose of 15 mg/kg monthly (every 30 days) during the RSV season. A maximum of 5 doses is generally sufficient prophylaxis during one season.\(^5\) Other monoclonal antibody (mAb) variants derived from palivizumab are being evaluated in clinical trials for immunoprophylaxis includes Motavizumab, a second-generation mAb, and Numax-YTE, a third-generation mAb.\(^3\)

In summary, bronchiolitis remains the most common cause of hospitalization in infants especially in winter. Although, it is mostly self-limiting requiring only supportive treatment, in selected high risk cases judicious use of newer therapies may be beneficial. Further robust clinical studies are necessary especially to reduce the hospital burden and save lives from severe form of bronchiolitis.

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**References**


