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Review Article

Bronchiolitis: State-of-the-art

ARM LUTHFUL KABIR

Abstract

The commonest cause of respiratory distress in young children is bronchiolitis. Bronchiolitis is an acute viral lower respiratory tract infection which predominantly affects children up to two years of age. It is a seasonal disease, dominating winter months, with a peak over 6 to 8 weeks around the winter solstice. The evidence and guideline recommendations consistently support a clinical diagnosis with the limited role for diagnostic testing for children who present with the typical clinical features of viral upper respiratory infection progressing to the lower respiratory tract. Management is largely supportive, focusing on maintaining oxygenation and hydration. Evidence suggest no benefit from bronchodilator or corticosteroid use in infants with first episode of bronchiolitis. Evidence for other treatment such as hypertonic saline is evolving. In case of severe bronchiolitis, there is some role for high-flow nasal cannula and continuous positive airway pressure use.

Introduction

Acute bronchiolitis is one of the most substantial health burdens for infants and young children worldwide[1] and is the commonest cause of respiratory distress in young children in Bangladesh.[2] The diagnosis of bronchiolitis is mostly clinical. Very simply, the first attack of wheezing in a previously healthy child of less than 2 years of age is bronchiolitis.[3] A diverse criteria may be with coryza symptoms followed by rapid onset of wheeze, fever, tachypnea, chest retractions, crepitation, rhonchi with radiological evidence of chest hyperinflation.[4]The simplest and succinct clinical case definition of bronchiolitis may be clarified as respiratory distress associated with cough, wheeze or crackles on auscultation having radiological hyperinflation and /or increased translucency having no definite evidence of consolidation in an infant below 2 years of age.[5]

The term "Bronchiolitis" was first coined in Bangladesh in the year 2001 following an outbreak of bronchiolitis in the winter and spring (2000-2001) in Bangladesh.[6] In fact, bronchiolitis is the leading cause for infants younger than one year of age to attendhospitals.[7,8] In a recent study, among a total of 5157surveyed under five children 3484 (67.5%) had respiratory problems. The most common cause of respiratory distress was bronchiolitis (21%),followed by pneumonia (11.5%), and asthma (8%) diagnosed by the trained research clinicians.[2] In the United Kingdom, using primary care database, the one year incidence of children given a specific diagnosis of bronchiolitis is 58 to 65 per 1000 children rising to 204 per 1000 when a broader definition of bronchiolitis was used to capture potential cases.[9] 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 in other countries such as Spain[10] and across health care systems,[3] with evidence that a diagnosis of bronchiolitis is more likely to be made in secondary than primary care. Admission to hospital with RSV bronchiolitis is typically around 2.4% of all infants[11,12] though in previously healthy term infants, the admission rate to hospital can be as low as 0.7%[13]. The median age of children is 3.0 months 83% are below 6 months of age. There are more male than female children affected with bronchiolitis.[3]

Sometimes, bronchiolitis was found to be positive for RSV virus in 49%[3] to 63% cases.[8] The incidence peaks during winter and early spring. In tropical countries, occurrences of RSV bronchiolitis tends to coincide with rainy season. Mortality for bronchiolitis is low, less than 1% in United States[14] and 2% in Bangladesh.[3]

Correspondence: Prof. ARM Luthful Kabir, Professor of Paediatrics, Ad-din Women's Medical College, Dhaka. Phone: 01711185409, E-mail: edrafed@gmail.com
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Bronchiolitis is generally a self-limited disease for most previously well infants. There are several individual and environmental risk factors that can put children with bronchiolitis at risk of severe disease. The risk factors are male sex, young age between 1-3 months[15], preterm infants, male sex, being bottle-fed, multiple birth, chronic lung disease of prematurity, hemodynamically significant congenital heart disease (HS-CHD), hemodynamically non-significant CHD, cardiomyopathy, congenital abnormalities of nervous system, trisomy 21, neuromuscular disorders, cystic fibrosis, immunodeficiency, cerebral palsy, bronchopulmonary dysplasia, congenital lung disease and/ or bronchial abnormalities, pulmonary hypertension, solid organ and stem cell transplant.[16-20] Several preventable environmental risk factors for severe bronchiolitis are cigarette smoke, in utero tobacco smoke exposure.[21] Air pollution may also increase the risk for bronchiolitis.[22]

Etio-pathogenesis

The most common etiology of bronchiolitis is Respiratory Syncytial Virus (RSV), accounting 43-75% cases.[23,24] In Indian subcontinent, the outbreaks occur from September to March. Ninety percent of children are infected with RSV in first 2 years of life, and up to 40% will develop lower respiratory tract infection during the initial infection.[25-27] Other viruses that cause bronchiolitis include human rhinovirus, human metapneumo virus, influenza, adenovirus, corona virus, parainfluenza viruses and human boca virus.[23,24,28,29] RSV has two strains, A and B with RSV A associated with more severe disease.[30,31] Reinfection in the same season with the same or different strain is possible.[3] As a sole infecting agent, RSV is associated with more severe bronchiolitis than other single respiratory virus infections.[32] Molecular diagnostic techniques have also revealed a high frequency (15-25%) of mixed viral infection among children evaluated for bronchiolitis.[33-35] Co-infection of RSV with rhinovirus can produce even more severe disease.[36] 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.[37]

RSV transmission occurs from person to person either by direct inoculation of nasal mucosa with contaminated secretions or by inhalation of large infectious droplets. Virus replicates in the nasal epithelium, and an exaggerated immune response occurs. After an incubation period of 4 to 6 days from transmission, upper respiratory symptoms appear, including nasal congestion and rhinorrhea.[15]In approximately one-third of infected patients, infection spreads to the lower respiratory tract by sloughing and aspiration of necrotic nasopharyngeal epithelial cells. Viral replication subsequently occurs in the mucosal epithelial cells of the bronchioles. The resultant immune response in the lower respiratory tract involves a combination of airway edema, increased mucus production, and necrosis of the airway epithelial cells due to direct cytotoxic injury leading to airway narrowing.[38] The airway narrowing is further worsened by impaired ciliary function. Cough, wheezing, tachypnea, nasal flaring and retractions are the clinical manifestations of the airway obstruction. Distal air trapping causes hyperinflation and localized atelectasis. Mismatching of ventilation and perfusion leads to further increased work of breathing and hypoxemia. Fever is not universal, occurring in approximately 50% of patients. An uncomplicated illness may last 1 to 3 weeks before all symptoms are completely resolved, although viral shedding may last up to 4 weeks, especially in very young or immunecompromized patients.

Clinical features

The symptoms of bronchiolitis are: cough, runny nose, nasal blockade, cough with vomiting, breathing difficulty, feeding difficulty, sleeping difficulty, restlessness, inconsolable cry, hoarse voice, no social smile, cyanosis, impaired consciousness, and rarely convulsion. Fever is typically below 39p C, although fever above 38.5p C is seen in 50% of infants.[5,39]

The signs are wheeze, bloated chest, chest in-drawing, nasal flaring, intercostal recession, fever (low grade), tachypnea, hyperresonance on percussion, tachycardia, rhonchi, crepitation, palpable spleen and palpable liver, hypoxemia (SPO2 < 90%), grunting, conjunctivitis, URTI features-conjunctivitis, pharyngitis, otitis media, apnea, respiratory failure and dehydration.[3,20] Apnea may be a presenting sign, sometimes in the absence of other features of bronchiolitis and this apnea may be a potentiallylife-threatening complications of bronchiolitis in young infants.[40] 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.[41,42] Respiratory rate is a key marker of disease severity,

with ≥60/min considered severe and e"70/min is critical.[43,44] Children tend not to relapse during the improving phase of the illness, which should give confidence to clinicians when considering discharge from emergency department or hospital ≥60/ min.[45,46]

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 (SpO2 < 95%) from severe (< 93%) and very severe RSV disease (SpO2 < 90%), inability to feed orally, or reduced level of consciousness.[47] Severe forms of bronchiolitis caused by RSV or other respiratory pathogen may frequently be complicated by acute encephalopathy presented with seizure or other neurological manifestations.[48]

The clinical features may be grouped into chesty features such as cough, breathing difficulty, chest in-drawing, wheeze, tachypnea, tachycardia, rhonchi and crepitation and non-chesty features such as feeding difficulty, sleeping difficulty, social smile, restlessness, inconsolable crying, nasal flaring, hypoxemia and fever. The chesty features demonstrate gradual recovery (after 4 days of admission) and non-chesty features demonstrate rapid recovery (within4 days of admission).[5] It is very interesting to note that in bronchiolitis, the return of social smile (a non-chesty feature) occurs in just 4 days over 90% of cases, but the chesty features of cough and wheeze continue beyond 4 days in a significant number of cases[5] resulting in a laughing, coughing and wheezing child.

Investigations

Pulse oximetry

Appropriate use of pulse oximetry monitoring and initiation of oxygen for bronchiolitis have received increasing attention. Otherwise stable infants with bronchiolitis may develop intermittent hypoxemia and arbitrary use of pulse oximetry threshold may result in unnecessary hospital admission.[49] A similar trial in the UK in the hospital setting found that reduction of the oxygen threshold from 94% to 90% resulted in earlier discharge from hospital without any evidence of adverse outcome.[50] Effects of Evidence supports recommendations in US practice guidelines that the clinicians use a threshold of 90% for initiation of oxygen whereas UK guidelines recommend 92%.[51,52] The target oxygen saturation of SpO2 ≥90% for discharge from hospital could be clinically effective considering the establishment of feeding, return of social smile, disappearance of hypoxemia and defervescence of fever.[53] So, the use of pulse oximeter should be in collaboration with monitoring of other clinical parameters.

Blood testing

Guidelines universally do not recommend CBC and blood culture in infants with bronchiolitis except very young infants of 1-2 months with fever.[54,55] Bacteremia is exceedingly rare in both febrile and afebrile bronchiolitis.[56] Urinary tract infection (UTI) in infants with bronchiolitis occur with greater frequency than do bacteremia and meningitis. It is reasonable to obtain a urinalysis and urine culture for infants less than 60 days with fever and for older febrile infants who have risk factors for UTI.[55] However, urine should not be routinely obtained in all infants with bronchiolitis. The mean WBC count is within normal limits, with mean 10,717/cmm, polymorphs 44% and lymphocyte 51%.[5]

Imaging

There is low prevalence of radiographic pneumonia (7%) i.e. airspace disease in bronchiolitis[57] and the majority of the children have radiographic findings consistent with simple bronchiolitis like hyperinflation, increased translucency, increased interstitial markings, streaky densities, peribronchial cuffing, perihilar infiltration, ground glass opacity (interstitial infiltrates), dirty lungs, collapse, confluence of opacities, patchy opacity, consolidation, increased retrosternal space or even normal.[58-60] Factors that have been associated with definite focal alveolar infiltrates consistent with pneumonia include hypoxemia (SPO2 < 92%), grunting, persistently focal crackles, and fever (especially > 39p C.[51,60] Chest radiographs should only be considered in patients when the presentation is not classic for bronchiolitis. Lung ultrasound is increasingly used to assess cardiopulmonary conditions in adults and children. Studies are coming up showing that ultrasound findings in infants with bronchiolitis correlate with clinical findings and might be more specific than chest radiography.[61,62]

Viral testing

Many national guidelines recommend against routine virological testing in bronchiolitis. Virological testing

does not generally assist in management and is insufficient to predict outcome.[63] Studies suggest that higher respiratory syncytial virus genomic load, measured using quantitative PCR, might be associated with increased length of stay, use of respiratory support and the need for intensive care, in addition to recurrent wheezing, compared with lower viral loads. [64-66]

Diagnosis

Bronchiolitis is a clinical diagnosis based on history and physical examination according to consensus across national guidelines. The diagnosis has a typical onset of a viral respiratory tract prodrome proceeding to lower respiratory syndrome over 3 to 4 days. So, the diagnosis may be stated as "runny nose followed by respiratory distress (either tachypnea or chest recession or both) associated with cough, rhonchi or crackles on auscultation in a child below two years of age."[5,51] Additional considerations are chest radiology of hyperinflation or increased translucency.[5,32] Fascinatingly, laughing, coughing and wheezing (whistling sound from chest) in a lap baby (small infant) may be viewed as bronchiolitis.[67]

Differential diagnoses

The differential diagnoses include viral pneumonia, viral induced wheeze / wheezy bronchitis.[68,69] Bacterial pneumonia is characterized by persistent crackles(crepitation) in one lung zone, fixed focal wheeze, persistent pyrexia (> 39°C) or persistently increased work of breathing. Other uncommon differential diagnoses are congenital heart disease when pulmonary vascular resistance falls increasing left to right shunt. Pulmonary malformations like fixed focal wheeze may be a sign of tracheomalacia, bronchomalacia, stenosis or compression from congenital lobar emphysema or a bronchogenic cyst which would warrant a chest imaging for further evaluation. A slow recovering course with persistent chest signs could be infected congenital cystic adenomatoid malforfation (CCAM), pulmonary sequestration. Children with persistent fine crackles, tachypnea, and hypoxemia may have interstitial lung disease (neuroendocrine cell hyperplasia of infancy, NEHI) presenting as recurrent "bronchiolitis". Post infectious bronchiolitis obliterans (PIBO) is manifested with persistent and sometimes focal crackles following adenovirus or other respiratory viruses and mycoplasma pneumonia.[20]

Management

In most children, bronchiolitis can be managed at home by parents or caregivers. There is widespread variation across hospitals and countries in the management and treatment of bronchioitis reflecting local custom and individual clinical practice.[70] There are many guidelines which have been updated as a critical review.[71] No therapies receive support across all guidelines for use with the exception of supplemental oxygen.

Supportive therapies

Supportive therapies include nasal suctioning, hydration and chest physiotherapy. Nasal suctioning: As children are obligate nasal breathers, superficial nasal suctioning has been suggested to help the clearing of nares, improve the work of breathing and improve feeding.[44] However, deep suctioning and frequent suctioning might increase length of stay of inpatients[72] and oxygen saturation might increase after suctioning.[73]

Hydration*:* Infants with bronchiolitis might have difficulty feeding because of nasal congestion and increased work of breathing: thus hydration remains a corner stone of therapy. Most guidelines recommend either nasogastric or intravenous fluids (isotonic fluids) to maintain hydration. A nasogastric tube might be easier to place than an intravenous line in children with bronchiolitis.[74] UK and Scottish guidelines preferring nasogastric or orogastric hydration in those that can tolerate it compared with intravenous hydration.

Chest physiotherapy: Chest physiotherapy appears to vary by country. A Cochrane Collaboration review demonstrated no evidence of benefit to any type of chest physiotherapy among inpatients in length of stay, oxygen saturation or respiratory parameters.[75]

Home treatment

Directed at relieving stuffy nose, ensuring hydration and nutrition, alleviating fever and recognizing development of 'red flag' symptoms (worsening of work of breathing, reduced fluid intake or no wet nappy for 12 hours, apnea or cyanosis and exhaustion).[51]

Indications for hospitalization-if the child has any of the following:

(a) Apnea (observed or reported)(b) persisting severe respiratory distress for example grunting, marked chest recession, or a respiratory rate over 70 breaths per minute (c) inadequate oral fluid intake (50-75% of usual volume) taking account of risk factors and using clinical judgment (d) persistent oxygen saturation of less than 92% when breathing air.[51]

Oxygen therapy

Oxygen may be used to treat hypoxemia SpO2 <92%). The threshold oxygen saturation at which to use supplemental oxygen varies across guidelines and is typically set between 90% and 94% at sea level. Children admitted to hospital with bronchiolits, management at a threshold of 90% SpO2 is safe and as clinically effective as a 94% target.[50,53] Many infants discharged home from ED experience desaturation events subsequently that are not associated with clinical deterioration.[76, 53] Suspect impending respiratory failure if the child has any of the following: (a) signs of exhaustion, for example listlessness or decreased respiratory effort (b) recurrent apnea (c) failure to maintain adequate oxygen saturation despite oxygen supplementation. The child may need PICU care.[51]

High flow oxygen and respiratory support

Non-invasive technologies to improve oxygenation and ventilation for bronchiolitis include high-flow nasal cannula(HFNC) oxygen and continuous positive airway pressure (CPAP).[77] Recent years have seen the increasing use of HFNC oxygen in acute bronchiolitis.[78] Evidence for efficacy of HFNC is predominantly observational with studies documenting improved respiratory parameters and reduced intubation rates after implementation. CPAP has been studied in ICU settings in observational studies and several small trials with some evidence of improved respiratory parameters. The UK guidelines recommend use of CPAP in children with impending respiratory failure from bronchiolitis.

Bronchodilators

The role of bronchodilators for the treatment of bronchiolitis have found no consistent benefit in any outcome for infants admitted to hospital in terms of improvement of clinical scores, and oxygen saturation compared with placebo.[79] The role of nebulized epinephrine was also similar compared with placebo considering the length of stay and other outcomes.[80]

Nebulized hypertonic saline

Nebulized hypertonic saline (3%) is thought to reduce airway edema, decrease mucus plagging, improve mucociliary clearance and rehydrate the airway surface liquid in infants with bronchiolitis.[81] Some trials that showed the largest benefit were done in hospitals with reducing the lengths of stay and risk of admission to hospital.[82] No substantial adverse effects of hypertonic saline were noted in the review. However, reanalysis of the review after resolving the heterogeneity failed to demonstrate any benefit for hypertonic saline over normal saline.[83] The conflicting results reflected in the differences in recommendations across national guidelines with some countries not recommending hypertonic saline, some recommending use in all inpatients and some recommending use only in moderate to severe cases.

Corticosteroids

Studies have shown no benefit to corticosteroids alone in reducing admission rate, resolution of clinical symptoms, and reduction of length of hospital stay for infants with bronchiolitis.[84] Clinicians report the use of corticosteroids considering a family or personal history of atopy when deciding to treat infants with bronchiolitis.[85]

Antibiotics

Clinicians feel urged to use antibiotics because of concerns about the presence of fever, the young age of the affected children, difficulty in differentiating atelectasis from infectious consolidation on chest radiograph and concern for undetected secondary bacterial infection. Bronchiolitis, however, has a clear viral cause and the occurrence of secondary bacterial infection is low with a risk of bacteremia or meningitis of less than 1%.[56,86] The routine use of antibiotics did not improve the duration of symptoms, length of hospital stay, need for oxygen therapy or hospital admission.[51]It was also shown in another RCT conducted with three arms, comparing parenteral, oral and no antibiotics that managing acute bronchiolitis without antibiotics in adjunct to supportive measures remains preferable as the clinical outcome is similar in terms of clinical features, length of hospital stay and the need for oxygen therapy to those cases requiring abtibiotics.[5] That overuse of antibiotics is known to result in unnecessary adverse effects on the patient and the development of antimicrobial resistance.

Antivirals

Currently, the only antiviral drug approved for the infection is ribavirin; however, its use is limited due to adverse side effects and the risks it poses to healthcare providers. Moreover, several drugs have been routinely administered for years in infants with acute RSV bronchiolitis, even if their efficacy is often not confirmed by clinical evidence, and studies on emerging antiviral drugs are still ongoing.[87,88]

Preventive therapy

Premature infants or infants with co-morbidities (such as hemodynamically significant heart disease, immunodeficiency, or neuromuscular disease) should receive prophylaxis with palivizumab as appropriate during RSV season as per AAP guidelines[77].In the clinical setting, appropriate isolation precaution measures should be used to minimize spread of infection to other patients or caregivers. Appropriate hand hygiene (using alcohol-based hand rubs or soap water) and decreasing exposure of young infants in particulars to others who are ill. Decreasing tobacco exposure as well as breast feeding should be encouraged.

Prognosis and counseling

Bronchiolitis is a self-limited disease with a relatively good prognosis. Improvement occurs by 4 days[5] though a characteristic harsh cough may persist for 21 days or more[19].Mortality is relatively low and declining in otherwise healthy children, including those younger than one year[14,,38]. The most common sequela attributed to bronchiolitis is the development of reactive airway disease (RAD) or asthma later in childhood. The risk varies from 20% to 60%[89,90]. Asthma may occur with increased frequency in infants with a personal or family history of atopy. Therefore, counseling to all families after the initial episode of bronchiolitis should include advice to be attentive to the potential for wheezing or increased respiratory distress if the child develops another viral respiratory illness in future.

Conclusion

Bronchiolitis is the commonest cause of respiratory distress of young children below one year. The diagnosis is clinical with cough, respiratory distress and wheeze. Pulse oximeter is essential to measure the oxygen saturation of blood and monitoring of oxygen therapy. Hydration and nutrition are to be maintained. Nebulized hypertonic saline may be tried as mucolytic agents. There is great scope of limiting the indiscriminate use of antibiotics if we can meticulously diagnose bronchiolitis with correct understanding of chest x-ray features of hyperinflation, increased translucency and no definite evidence of alveolar infiltrates. Parents are to be counseled about the possibility of recurrent attacks of bronchiolitis, reactive airway disease (RAD) and asthma in future.

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