REVIEW ARTICLE

BRONCHIOLITIS: THE RECENT EVIDENCE

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Bronchiolitis is an active area of research across the spectrum from genetic mechanisms to population-based research. Surveillance studies are identifying new causes of bronchiolitis and exploring the role of viral co-infections. The studies have revealed that comorbidities are an important determinant to predict the course of the illness. Also the specific physical findings and diagnostic tests used to predict the outcomes in bronchiolitis do not have high predictive value. The pulse oximetry, probably, is a double edge sword. It has contributed to better childcare but is also likely contributing to longer hospitalizations and greater use of health care resources. The available data is yet largely against the routine use of bronchodilators or corticosteroids, though a combination of these two looks promising future trend. The role of nebulized hypertonic saline in bronchiolitis is getting a wider acceptance and is likely to get established a part of routine care.

Keywords: Bronchiolitis, Bronchodilators, Corticosteroids, Nebulized hypertonic saline

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INTRODUCTION

Like many other developing countries, the comprehensive community based, etiological, epidemiological and interventional studies about bronchiolitis are lacking in Pakistan. The financial constraints limit the research for the aetiologic agents, diagnostic workup or management interventions. Till the time we have our own data, we will remain dependent on American and Western research for the understanding of various aspects of bronchiolitis. Yet to start with, we can start developing local guidelines for managing our children with this disorder. The present review is a step towards this direction. As the bronchiolitis is an active area of research in the developed world, and many important studies have advanced our understanding of this disease so in this review, we will overview the current evidence on the pathophysiology, aetiology, epidemiology, clinical presentation, the diagnostic workup and the modalities available for managing this problem. The prevention is an important area but we plan not to touch it.

Bronchiolitis is a well-recognized clinical syndrome.[1] Clinically it presents with rhinitis, cough, tachypnea, use of accessory respiratory muscles, hypoxia, and variable wheezing and/or crackles on auscultation. The evaluation and management of bronchiolitis varies substantially. The viral isolation, blood serology, and chest radiographs often are ordered, although they have little impact on diagnosis. Most clinical interventions have no significant impact on length of hospital stay, severity of clinical course, or subsequent outcomes such as episodes of recurrent wheezing or ultimate diagnosis of asthma.[2] It is not amazing, in the presence of conflicting data[3–5], that no consensus was developed before 2006. The American Academy of Paediatrics (AAP) published, for the first time, the guidelines to deal with the bronchiolitis.[6]

Definition and Pathophysiology

The term "bronchiolitis" refers to the inflammation of the bronchioles but the inflammation of the bronchioles is usually not observed directly. It is presumed to be present in a young child who presented with respiratory distress along with the signs of a viral infection.[7] As the definition of the bronchiolitis varies so it is no wonder that there is so much variability in the clinical evidence derived from the published studies. In the United Kingdom, a consensus definition was derived as "a seasonal viral illness characterized by fever, nasal discharge, and dry, wheezy cough. On examination there are fine inspiratory crackles and/or high-pitched expiratory wheeze.[8] The North Americans use the term bronchiolitis more broadly but do stress the specific finding of wheeze. The AAP guidelines have defined bronchiolitis as "a constellation of clinical symptoms and signs including a viral upper respiratory prodrome followed by increased respiratory effort and wheezing in children less than 2 years of age".[6] This distinction is important as viruses like rhinoviruses that are typically limited to the upper respiratory tract often trigger the recurrent wheeze in older children. Therefore the researchers have tried to limit the term bronchiolitis to the infants younger than one year with a first-time episode of wheezing. But yet the heterogeneity in the phenotype of the disease is not fully comprehended.

It is important to understand the pathophysiological changes leading to bronchiolitis as that provides the basis to realize the development of clinical manifestations and to develop a rationale management plan.[9] It begins with the acute infection of the epithelial cells lining the upper respiratory tract by the viruses and then travel down to the lower within a few days. This results in the inflammation of the bronchiolar epithelium, with peri-bronchial infiltration of white blood cell types, mostly mononuclear cells, and

oedema of the submucosa and adventitia. The oedema, increased mucus production, fibrin and plugs of sloughed, necrosis and regeneration of the epithelium in the airways cause partial or total obstruction to the airflow. The airways keep clearing at one site and getting blocked at others so the site and degree of obstruction varies. This explains the rapidly changing clinical signs and the difficulty in accurately assessing the severity of the illness over the time.[2] A "ball-valve" mechanism can lead to air trapping distal to obstructed areas with subsequent absorption resulting in atelectasis. Obviously hypoxemia results because of these atelectatic areas that are not ventilated any more. The hypoxemia is further compounded by the lack of collateral channels in young children and iatrogenically by the administration of high concentrations of supplemental oxygen, which is absorbed more rapidly than the room air.[10] Smooth muscle constriction does not seem to have much role in the pathologic process and that may explain the limited benefit of bronchodilators observed in various clinical studies.[11]

Aetiology

The list of etiological viruses is expanding with the availability of molecular amplification techniques that are much more sensitive. Respiratory syncytial virus (RSV) usually accounts for 50–80% of cases.[11,12] Other causal viruses include the para-influenza viruses, primarily para-influenza virus type-3, influenza, and human metapneumovirus (HMPV).[13,14] HMPV is considered to account for 3–19% of bronchiolitis cases.[15,16] The clinical course of RSV and HMPV seems to be similar. Most of the children are infected during annual widespread winter epidemics and a subset develops bronchiolitis.[13,17,18]

The new data reveals that young children with bronchiolitis are often infected with more than 1 virus.[19] Rates of co-infection range from 10–30% in samples of hospitalized children, usually with RSV and either HMPV or rhinovirus.[20,21] There are controversies over the question whether the concomitant infections are associated with increased severity of the bronchiolitis or not. The published data has shown a 10 fold increase in the risk of mechanical ventilation associated with dual RSV and HMPV infection[22] while others have revealed no increase in severity with dual infections with viruses[21,23].

The rhinoviruses are well known for triggering exacerbations of wheezing in older children with reactive airway disease or asthma but as a cause of bronchiolitis their role is not wel-documented[24–26], though one study has revealed that more of children under 2 years being affected with rhinovirus bronchiolitis are black, have a previous history of wheezing or have been treated with corticosteroids.[12]

The emerging research on genomics of bronchiolitis has identified single nucleotide polymorphism in a number of genes, including those involved in innate immunity, that are associated with risk for more severe bronchiolitis.[27,28] There are other genes like vitamin-D receptor genes that are associated with bronchiolitis and may provide an evidence to link neonatal vitamin-D level with wheezing in young children.[29–31] Also parental and household smoking has been demonstrated to increase the risk of bronchiolitis.[32]

Epidemiology

Bronchiolitis is an acute, highly contagious disease of the lower respiratory tract of infants with the highest incidence in the winter in temperate climates, and in the rainy season in warmer countries.[33,34]

Bronchiolitis all over the world, is the leading cause of the infants' visit to the doctors. In United States, this is the leading cause of infant hospitalization and is associated with progressively increasing morbidity and cost of treatment over the last few years.[20,35,36]

The studies over time have shown that there is high degree of morbidity in bronchiolitis but mortality is low. Usually around one third of children do develop bronchiolitis in their first 2 years.[37] The hospitalization rates vary from 3% to over 7%, depending upon the type of infant population being studied.[38] The data from USA shows that the mortality rate from bronchiolitis is low.[39,40] Most deaths in bronchiolitis occur in infants younger than 6 months of age. In previously well children, bronchiolitis is usually a self-limiting disease that responds well to supportive care within the home. However, young infants and those having pre-existing medical conditions form a vulnerable group that may need inpatient admission.[2] The premature, infants with underlying cardiopulmonary diseases or with immunodeficiency disorders are more at risk.[41]

The commonest risk factor for hospitalization is age.[42] Most admissions are in younger than 1 year of age, while infants below 3 months are at increased risk of apnea and severe respiratory distress.[43] Prematurity and Caesarean section is another risk factor for severe bronchiolitis, especially with a previous history of neonatal respiratory distress syndrome.[44] Patients with unrepaired congenital heart disease, especially with pulmonary over-circulation, and children with chronic lung disease have diminished pulmonary reserve, thus increasing the hospitalization rate in such children.[45] Children born with airway abnormalities such as laryngomalacia, tracheomalacia or cleft lip/palate usually need supportive care to clear off the upper airway secretions. Also the children with neurologic abnormalities associated dystonia may need additional support for managing secretions.[46] The infants older than 60 days, having bronchiolitis and fever, have low risk of serious

bacterial infection (SBI) while those younger than 60 days require a full septic screen for urinary tract infection, meningitis and bacteremia.[43]

But the evaluation and treatment for sepsis is associated with parental dissatisfaction, increasing antibiotic resistance, and iatrogenic complications. For very young febrile infants who have obvious bronchiolitis, there are no current guidelines for the management. Based on the current literature, the risk of SBI among infants younger than 30 days remain substantial and they should continue to have full evaluation for SBI and administration of empiric antibiotics.[47–51]

The prophylactic immune therapies like palivizumab have shown a decrease in RSV related hospitalization rates for specific high risk groups.[52,53] Accordingly AAP did modified its recommendations, recently.[54]

Presently there is a lot of research to find out the risk factors associated with the development of severe bronchiolitis[55] and attempts are continued to identify the clinical predictors of hospitalization in outpatient population.[56] The data demonstrates that individual clinical findings on physical examination have limited predictive value in terms of outcome. This may be because of the typical minute-to-minute variability of these findings among children with bronchiolitis. Considering independently, other predictors including atelectasis on chest radiography, have shown a co-relation with outcomes and overall clinical severity but does not add much to the assessment of such children.[56] An important variable to provide anticipatory guidance for management or to decide about admission and discharge is the "Day of illness" as characteristic pattern in bronchiolitis will lead to the progressive worsening of symptoms peaking around day 3 or 4. A recent paper has shown that the unnecessary care for bronchiolitis (antibiotic use and steroid administration) decreases with an increase in the prevalence of inpatient children with bronchiolitis.[57]

Pulse oximetry measurement has been the most promising to predict the outcomes of bronchiolitis[58] . We know from the pre-pulse oximetry era that mild hypoxemia is correlated with more severe course of the disease that probably is because of pulmonary ventilation to perfusion mismatch.[59] Changing the arbitrary thresholds for oxygen therapy may influence the outcomes. There would be a significant increase in hospitalization if the cut off value for pulse oximetry is chosen 92%.[6] Also there are substantial number of children who need oxygen when other abnormalities have improved and so remain hospitalized for oxygen need.[61] A British study has tried to assess this aspect and has shown that the mean lag time for oxygen saturation to normalize was 66 hours after all other problems had resolved[62]. It is, therefore, best to monitor the pulse oximetry continuously as this would detect the characteristic transient dips in oxygenation associated with bronchiolitis. It seems quite obvious why AAP has supported that the oxygen therapy be initiated judiciously when oxygen saturation levels fall below 90% and oxygen monitoring can be reduced once the infant starts improving.[6] The future seems to be more promising with studies coming up on use of home oxygen therapy in children with bronchiolitis.[63,64]

There is always a danger of apnea in young infants with bronchiolitis, especially those with RSV. The incidence may vary depending upon the various factors but is usually around 3%.[65,66] The risk factors included a previous history of apneic episode and age less than one month for full term infants or 48 weeks post conceptional age for premature infants.[65]

Diagnostic Work-Up

The diagnosis in most cases of bronchiolitis is clinically evident and does not require diagnostic testing. Patients usually report a history of recent upper respiratory tract symptoms. Lower respiratory tract symptoms such as cough, tachypnea, and increased work of breathing follow the upper respiratory prodrome. There is nasal congestion, rhinorrhoea, cough, tachypnea, and increased respiratory effort that is evident by nasal flaring; grunting; and intercostal, supra-costal and subcostal retractions. The work of breathing falsely increases significantly with nasal obstruction so nasal suctioning and repositioning may allow a better assessment of lower respiratory tract involvement that may be revealed by a variety of auscultatory findings like crackles, wheezes, or referred upper airway noise. The most sensitive and earliest sign is the fast respiratory rate. The apnea alone may be the presenting sign in premature young infants or a complication of bronchiolitis. A child can present with mild tachypnea to impending respiratory failure. A significant variability between serial examinations is common owing to dynamic nature of the disease. The tachycardia may develop due to dehydration and variable degrees of hypoxemia. The minimum assessment includes respiratory rate, work of breathing and hypoxia.[2,47,67]

But the clinician has to be vigilant because of broad range of differential diagnosis such as viral bronchiolitis ,other pulmonary infections (e.g., pneumonia, mycoplasma, chlamydia, tuberculosis) laryngo-tracheomalacia, foreign body, (oesophageal or aspirated), gastro-oesophageal reflux, congestive heart failure, vascular ring ,allergic reaction ,cystic fibrosis, mediastinal mass, bronchogenic cyst and

tracheo-oesophageal fistula. In the presence of atypical features such as the absence of viral symptoms, severe respiratory distress, and frequent recurrences children may require diagnostic evaluation to rule out other causes.[33]

There is no consensus among clinicians for the work up of bronchiolitis. The practice varies widely especially for viral detection and radiography.[3] The evidence to date does not suggest any role for diagnostic testing in the management of routine cases of bronchiolitis.[6,54,67] The studies have shown that if the care of bronchiolitis be standardized, there can be substantial reduction in diagnostic testing rates saving lot of costs without jeopardizing outcome.[68,69] The evidence does support only a limited role for diagnostic testing in the diagnosis of bronchiolitis.

The antiviral agents are not recommended for the management of bronchiolitis so isolation of specific causative virus is not required. There are tests available for the rapid viral antigen detection but they have variable sensitivities and specificity depending on the test used and when they are used, during the respiratory season.[68] The predictive values of these tests is generally good during the peak viral season but decreases considerably at times of low prevalence. As most viruses causing bronchiolitis have similar clinical course, the usefulness of the identification of the specific agent varies according to the setting. In a routine/typical outpatient case, results would probably have little impact on management. But in a hospital inpatient, specific viral identification may be used as a part of successful intervention to reduce the nosocomial infection[65,66] and patients infected by the same viral pathogen may be cohorted. The multiple studies have also shown that there is low rate of bacterial co-infection in cases of bronchiolitis except for RSV infection where, though the rate of co-infection is low but can't be said to be insignificant.[47,70] So the majority of the data supports that for most of the cases of bronchiolitis the clinical diagnosis is sufficient and viral testing adds little to the routine management.[71]

The routine use of chest radiography for the diagnosis and management of bronchiolitis is not recommended[6]. The radiographs in children with bronchiolitis often show hyperinflation, areas of atelectasis, and infiltrates but these findings are not associated with disease severity and do not guide management. The studies have consistently shown a low yield of routine radiography and a potential detrimental effect. Of 265 children with "simple" bronchiolitis (defined as coryza, cough, and respiratory distress accompanying a first episode of wheeze in a child without underlying illness), routine radiography identified findings consistent with bronchiolitis in only 2 cases, and in neither case the findings changed the acute management. After reviewing the abnormal findings in the radiographs, the clinicians were more tempted to treat with antibiotics for a perceived primary or a concurrent bacterial pneumonia, although the findings did not support that treatment because bacterial pneumonia rarely occurs in viral bronchiolitis.[72] The lung ultrasound is now being reported as a better and easy choice for the diagnosis of the bronchiolitis.[73]

Therapeutic Options

There are multiple therapeutic options[74] like bronchodilators, corticosteroids, antiviral agents, antibacterial agents, chest physiotherapy, nasal suction, and decongestant drops.[75,76] But all these interventions have not demonstrated any significant impact on duration of illness, severity of clinical course, or subsequent clinical outcomes, such as post-bronchiolitis wheezing.[77,11]

Supportive care: Newer recommendations emphasize supportive care with hydration and oxygenation as a primary intervention.

a) **Hydration:** The dehydration is consequent to faster breathing, copious secretions, fever and poor feeding and may require intravenous fluids or nasogastric feedings until feeding improves. The rehydration may be corrected with isotonic fluids as the release of antidiuretic hormone secondary to the bronchiolitis and administration of hypotonic fluids may lead to iatrogenic hyponatremia.[78,79]

b) **Feeding:** The infants whose nutrition is compromised with severe disease may be given nasogastric feeding until feeding improves. It has been shown that increasing protein intake of infants increases the anabolism in critically ill infants with bronchiolitis.[80]

c) **Oxygen:** Oxygen administration is a key therapeutic intervention. The goal is to maintain oxygen saturation to prevent hypoxia or insufficient delivery of oxygen to metabolically active tissue. A variable hypoxemia does occur in bronchiolitis from impaired diffusion across the blood-gas membrane and ventilation-perfusion mismatch caused by heterogeneous plugging of distal bronchioles. For most authors, pulse oximetry saturations higher than 90% are acceptable, as this saturation is associated with appropriate oxygen delivery on the oxy-haemoglobin dissociation curve. A complete assessment of the baby is required to decide for the need and duration of the supplemental oxygen. The oxygen may be discontinued once pulse oximetry saturations remains above 90% for most of the time and there is overall clinical improvement evidenced by the improved feeding and work of breathing. A clinically improving patient may experience intermittent decreases

in pulse oximetry saturation on day 3 or 4 of illness but that should not prompt automatic continuation or re-initiation of oxygen supplementation as that practice is associated with prolonged hospitalization and without significant benefits.[2,10,11]

There are no clear guidelines for cardiac monitoring or use of pulse oximetry in children with bronchiolitis. The cardiac monitoring can be considered for infants with underlying cardiac disease or those having episodes of apnea that is associated with bradycardia. The pulse oximetry is non-invasive tool providing rapid assessment of oxygenation but having a wide variability in its use and interpretation. Though pulse oximetry helps to decide about the need for admission, the extensive monitoring is associated with prolonged hospital stay and parents are not comfortable with this. The other disadvantages of pulse oximetry are motion artefacts, variation in product accuracy and falsely low readings in children with poor perfusion. The appropriate strategy is to monitor the oxygen saturation at regular intervals but children with cardiopulmonary problems, or having risk factors for apnea or who required continuous oxygen previously may be offered continuous oxygen saturation monitoring.

Bronchodilators:

The bronchodilators are abundantly used in the management of bronchiolitis at outpatients and inpatients facilities in our country and worldwide[81] so no surprise that their role in the treatment of bronchiolitis has been the subject of many studies and systematic evidence based reviews of literature.[82] It is an uphill task to compare these studies because of a wide range of study designs, a variety of therapies assessed and outcome measures that have ranged from short term improvement in clinical scores obtained soon after the intervention to a broader clinical outcomes such as need for subsequent hospitalization or duration of hospital stay or illness. Generally the score based studies are easy to compare but this is not the case in bronchiolitis because the scoring parameters used do not have established validity or proven correlation with clinically significant improvement.[83] Pooling the results of such large studies may result in a statistically significant difference that is of questionable clinical importance. In a Cochrane collaboration systematic review, studies that dichotomized patients into those who responded and did not responded to bronchodilators were compared (Figure-1).[82] The figure-1 shows heterogeneity of results that mirrors the responses among individual patients. A high rate of response (43%) seen in control subjects may result from clinical variability usually observed in bronchiolitis or from a response to other supportive measures and mistakenly being attributed to a bronchodilator response in an uncontrolled setting. The difference seen in the treatment group (57%) is not statistically significant. This questionable clinical response is underscored by a meta-analysis of studies that have found no effect of bronchodilator administration on hospitalization rates.[82,84] The other systematic Cochrane review of studies in 2006 reported a potential benefit with epinephrine administration in outpatients for management of bronchiolitis patients but other large, multi-centre studies have not confirmed this finding.34,85 So it is not advisable to use epinephrine in the outpatient setting due to limited data regarding safety with unmonitored administration. Overall the current evidence does not support the routine use of bronchodilators. A monitored trial of bronchodilators can be offered as an option but should only be continued after a documented beneficial response such as improvement in general condition, diminished work of breathing, low respiratory/pulse rate, improved hypoxemia as assessed with pulse oximetry.6

Corticosteroids:

Another area of controversy is the use of steroid for the treatment of bronchiolitis. Ambiguity regarding their use has arisen form a heterogeneous and difficult to interpret body of variably designed studies with variable sample size.[86] However, the studies with large sample size reveal that steroid administration is not associated with significant reductions in clinical scores, hospitalization rates or length of hospitalization.[6,87–89] On the other hand, steroids do have well established undesirable adverse effect profile. So steroids are no more recommended for the treatment of bronchiolitis. The studies[89,90] have noted that the children who received dexamethasone combined with 2 doses of nebulized epinephrine had a lower admission rate over 7 days than the placebo (17.1% Vs. 26.4 %). However this difference does not reach the statistical significance (p=0.07). The use of corticosteroids in synergy with adrenergic agents has been well established for asthmatic children.[91,92] But for bronchiolitis we need to wait further studies to confirm the same beneficial effect before this can be employed as a routine therapy for bronchiolitis.[90]

Anti-viral agents

Trials with ribavirin have demonstrated variable outcomes. The high cost, difficult administration and lack of robust evidence of benefit have limited the role of this therapy. Ribavirin may be considered for children with pre-existing diseases like organ transplantation, malignancy, congenital immune-deficiencies or patients who remain critically ill despite maximized support. The bronchiolitis by RSV represents a unique population that may be associated with influenza and its treatment with anti-influenza medications may lessen the severity and

complications, especially if started within 48 hours of start of symptoms but its initiation should only be considered if clinical picture and surveillance data of community is highly suggestive of influenza infection. The best option remains the annual influenza vaccination.

Antibacterial Agents:

There is no role for antibacterial agents in viral bronchiolitis[93,94] and they should only be used in patients with a concurrent bacterial infection[94,95]. The most common concurrent bacterial infection is acute otitis media (AOM).[96]

The antibiotic therapy should be based on patient age, severity of illness and diagnostic certainty. Patients younger than 6 months of age may receive amoxicillin 80 mg/kg per day divided into two doses for 7–10 days. Patients older than 6 months and younger than 2 years should receive treatment if diagnostic certainty is strong but may be kept under observation if severity of infection is low.[2]

Chest physiotherapy:

As the pathophysiology of bronchiolitis involves diffuse infection of the epithelial cells lining the small airways that leads to heterogeneous areas of perfusion-ventilation mismatch so regional chest physiotherapy does not provide any benefit[97] though for RSV bronchiolitis a short term relief may be expected with special maneuvers.[98]

Nasal Suctioning and Nasal decongestants:

The infants are comforted when nasal suctioning is performed to relieve nasal obstruction due to copious secretions and it improves their feeding too. But the "deep" or excessive suctioning of the lower pharynx has to be avoided because that is associated with nasal oedema which can lead to additional obstruction.[2]

No evidence supports the use of nasal decongestant drops to relieve upper airway obstruction. Because of the lack of efficacy and potentially harmful adverse effects nasal decongestants should not be used to treat bronchiolitis.

Leukotriene antagonists:

The leukotriene receptor antagonist, montelukast, has been evaluated as a potential candidate to treat bronchiolitis but does not seem beneficial in resolution of symptoms.[99,100]

Hypertonic Normal saline:

The Nebulized hypertonic saline has been associated, in recent randomized trials and in a Cochrane meta-analysis, with improvement in clinical score and duration of hospitalization.[101–105]

Other therapies:

The other therapies like helium/oxygen, nasal continuous positive airway pressure or use of surfactant for treating bronchiolitis are being assessed for use in critically ill patients, though their role as of now is not established.[33,106-108]

Prognosis:

Mostly the children with bronchiolitis recover uneventfully[11] and but a subgroup of around 40% develops subsequent recurrent wheezing episodes through 5 years of age while only 10% experience subsequent wheezing after 5 years.[109] Newer theories based on the immune system development, genetic predisposition, ecology of infectious agents[110] propose that post bronchiolitis wheezing has an underlying predisposition to the original RSV infection.[111]

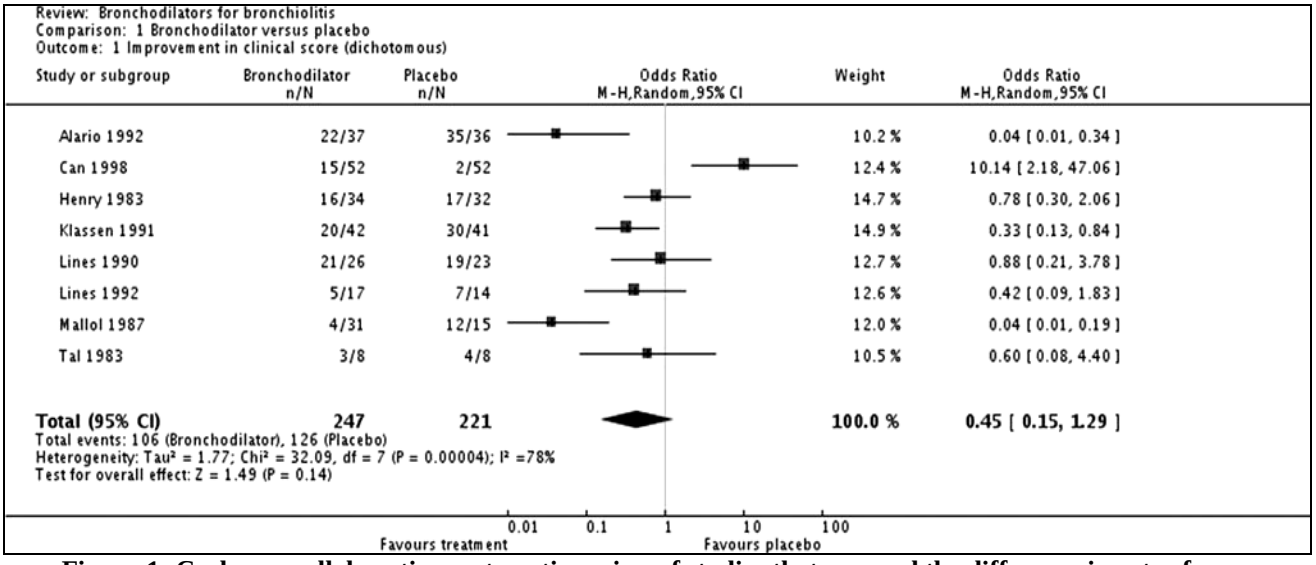

Figure-1: Cochrane collaboration systematic review of studies that assessed the difference in rate of improvement after B2-agonist bronchodilators or placebo among children with bronchiolitis. (reproduced from Gadomski AM, Bhasale AL. Cochrane Database Syst Rev. 2006;(3); CD001266.)

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