ORIGINAL ARTICLE

Management of Bronchiolitis- An Update

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ABSTRACT

Bronchiolitis is one of the most common respiratory infections in infants and young children predominantly caused by Respiratory syncytial virus. Most children have mild diseases, however bronchiolitis has also been well linked to severe morbidities and mortalities. Even though bronchiolitis is well recognized for many years, there are still very few therapeutic strategies available beyond supportive management. Furthermore, many controversies still exist regarding the best therapeutic management in bronchiolitis leading to numerous published clinical guidelines and research in this area. Management can be divided into pharmacological and supportive therapy. Evidence suggests that the current management of bronchiolitis is purely supportive consisting of oxygen supplementation and maintaining good hydration and nutritional support. With regards to pharmacological therapy, neither bronchodilators nor corticosteroids have significant efficacy in the treatment of bronchiolitis. However, some suggest that Epinephrine and nebulized 3% saline showed some benefit only in short-term outcome. Current recommendation also supports the use of Palivizumab as prophylaxis in certain group of infants and young children.

Keywords: Bronchiolitis, Respiratory syncytial virus, nebulized epinephrine, nebulized 3% saline,

INTRODUCTION

Bronchiolitis is one of the most common causes of serious lower respiratory tract infection in ininfants[1]. Respiratory syncytialvirus (RSV) is the most common organism[2]. This organism is responsible for about 60–85% cases of bronchiolitis[3]. Other organisms includemetapneumovirus[4] parainfluenza virus, Adenovirus, *Mycoplasma pneumoniae*have been associated with bronchiolitis. Bronchiolitis is characterized by acute inflammation, edema and necrosis of the epithelial cells lining the small airways, and increased mucus production[5]. The infectious process can produce symptoms like rhinorrhea, fever, cough, wheezing, respiratory distress, apnea, and hypoxemia.

Most children with bronchiolitis have mild disease and are managed at home with support from primary care providers alone[3]. Children with more severe symptoms nonetheless account for the majority of hospital admissions in the first 12 months of life and some will need ventilator support[6].

Children with pre-existing risk factors, such as prematurity, bronchopulmonary dysplasia, cystic fibrosis, congenital heart disease, structural or functional airway abnormalities, down syndrome, neuromuscular syndromes or immunodeficiency are at greater risk of more severe bronchiolitis as well as hospitalization and mortality[7].

Management: Even though bronchiolitis has been recognized by many years, still few therapeutic strategies are available beyond supportive ones and still many controversies exist regarding the best therapeutic management.

In 2006, the American Academy of Pediatrics (AAP) published a treatment guideline for bronchiolitis that remains the standard of care today[1]. Although use of the AAP's 2006 treatment guideline for bronchiolitis has demonstrated a significant reduction in the utilization of diagnostic and therapeutic resources, standardizing the treatment requires changing provider behavior, which is still a challenge[5].

Some clinicians believe the AAP guideline does not reflect routine practice, and implementation of the guideline remains highly variable. Provider treatment preference, rather than evidence-based practice, continues to be common. Management can be divided into pharmacological and supportive therapy:

PHARMACOLOGICAL THERAPY

Epinephrine: The combined α&β adrenergic properties of epinephrine are related to its potentially greater vasoconstrictor effects and the reduction of edema. Epinephrine appears to have the greatest short term benefits than the other bronchodilators. It

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provides better short-term improvement in the clinical score than placebo or albuterol, particularly in the first 24 hours. The risk of admission on first day is reduced significantly but has no effect on length of hospital stay[8].

Recent studies indicate that nebulized adrenaline can be effective in reducing the hospitalization rate among children presenting to Emergency Department, but it has no benefit in terms of reducing a patient's hospital stay[7].

Steroid therapy: Systemic and inhaled steroids have found to give no benefit in terms of reducing the hospitalization rates or hospital stays, or as regards patients' short- and long-term prognosis. Neither the duration of hospitalization nor the severity of symptoms is improved by inhaled or systemic corticosteroids [8].In addition, inhaled steroids given during the acute phase of bronchiolitis have no effect in preventing post-bronchiolitis wheezing[9].

Among inpatients, there was no benefit for the length of stay (LOS) for inpatients; however, there were significant differences between groups, favoring glucocorticoids for clinical scores at earlier points in time: three to six hours and 6 to 12 hours after admission[10].

Fernandez et al. compared the efficacy and safety of systemic and inhaled glucocorticoids (ICS) versus a placebo or another intervention. Among outpatients, glucocorticoids did not significantly reduce outpatient admissions at days 1 and 7 when compared to a placebo[11].

Combined epinephrine and corticosteroid therapy: Nebulized epinephrine combined with corticosteroids seems to be effective to reduce hospital admission within 7 days of a visit to the Emergency Department[12,13].

The available data on the effectiveness of combining adrenaline with high doses of dexamethasone cannot support the routine use of this treatment option and only further studies could clarify its real efficacy and long-term effects. The American Academy of Pediatrics (AAP) 2006 guideline reports that neither bronchodilators nor corticosteroids have significant efficacy in the treatment of bronchiolitis, which is supported by the current literature[14,15].

Salbutamol: The place of nebulized bronchodilators in treatment of bronchiolitis is controversial. Some authors reported that bronchodilators were as effective as an oral placebo in the management of bronchiolitis, while others found it safe and effective in relieving the respiratory distress of young infants[16,17].

Recent systematic reviews[18,12] confirmed that inhaled beta2-agonists are not useful in the treatment of bronchiolitis, thus supporting the AAP guidelines[7].

A Cochrane review of bronchodilators for bronchiolitis revealed that they provide small, short-term improvements in clinical scores. So, before making the decision to use bronchodilators for this small benefit, the costs and adverse effects of these agents should be considered[19].

The effects of bronchodilators (mainly nebulized albuterol) vs. placebo in infants were assessed by Gadomski & Scribani[14]. In 11 inpatient of random controlled trials (RCTs) and in 10 outpatient RCTs, the SpO2 (primary outcome) did not improve with bronchodilators. . The use of bronchodilators did not reduce the rate of hospitalization for outpatients, nor reduce the duration of hospitalization for inpatients[10].

Antibiotics: The effectiveness of antibiotics for bronchiolitis in children <2 years of age was evaluated by Spurling et al[20]. Five RCTs were included. The primary outcomes included time to resolution of signs or symptoms. One RCT found no significant differences between the ampicillin and placebo for length of illness. Two RCTs providing adequate data for hospital LOS showed no difference between macrolides and control. Two RCTs randomized children for IV ampicillin, oral erythromycin, and control, and found no differences for most symptom measurements (e.g., wheeze, shortness of breath, oxygen saturation, not smiling socially, fever & cough.

Ribavirin (Antiviral therapy): Antiviral drugs have no benefits in acute bronchiolitis[21]. No differences in long term pulmonary function or in incidence of recurrent wheezing following RSV infection were associated with the use of ribavirin[10].

Its use is not routinely recommended by current guidelines. According to a recent Cochrane review[22] there are insufficient data to provide reliable estimates on its effects in bronchiolitis. Given uncertainty about its effectiveness and the lack of data on its safety, this treatment option might be considered only for children with severe disease, or underlying conditions that predispose them to more severe presentation, such as immunodeficiency, chronic lung disease or complicated congenital heart disease (including pulmonary hypertension)[1].

Palivizumab: Palivizumab, the humanized monoclonal antibody, is capable of neutralizing RSV and has proved to be effective in reducing hospitalization rates relating to RSV infections[23,24,25].

The current recommendations of the American Academy of Pediatrics (AAP) for the management of bronchiolitis identify specific groups of children (<6-month-old preterm babies and <2-year-old preterm babies with BPD, children with significant congenital heart diseases featuring hemodynamic alterations, Children with cystic fibrosis and immunodeficiencies) found to be benefit from prophylaxis with palivizumab

and the minimal number of doses needed for an effective protection[1,26].

Prophylaxis to the whole population of children less than 24 months of age is impractical as it will be very costly[3].

Supportive therapy: Oxygen therapy, Nebulization with hypertonic saline, feeding and hydration, minimal handling and nasal suctioning are the important supportive cares.

Oxygen therapy: Oxygen supplementation remains the mainstay of treatment for bronchiolitis**.** Oxygen is administered via a heated humidified high flow nasal cannula (HFNC) has recently been introduced in clinical practice and is widely accepted even outside the intensive care setting as it has been proved to be a well-tolerated, non-invasive form of respiratory support[27,28,29].

The HFNC is thought to improve ventilator status by preventing mucus dryness and improving mucociliary clearance and delivering a continuous positive airway pressure, which helps to keep the alveoli patent, improves the ventilation perfusion mismatch, and prevents micro atelectasis[3]. In the UK, supplemental oxygen therapy is usually administered for oxygen saturations of less than 95% in air, whereas the American Academy of Pediatrics recommends its use only if oxygen saturations fall persistently below90% in previously healthy infants[30].

Hypertonicsaline: Nebulized 3% hypertonic saline is believed to improve airway hydration through osmosis (it causes water to move from the interstitium into the airway thereby decreasing interstitial edema mucosal viscosity), resulting to improvement in mucociliary clearance of airway secretions and effectively reduces the hospitalization stay among infants with non-severe acute viral bronchiolitis. It appears efficacious and safe if combined with a bronchodilator, and it improves clinical severit[31,32,33] score in outpatient and inpatient population[34].

Nebulized Hypertonic saline (HS) treatment significantly decreases the duration and rate of hospitalization compared with nebulized normal saline (NS). Furthermore, nebulized hypertonic saline treatment had a beneficial effect in reducing the clinical severity (CS) score of acute bronchiolitis in Infants post-treatment[35].

Frequently inhaled Hypertonic Saline (HS) relieved symptoms and signs faster than Normal Saline (NS), and also shortened length of hospital stay (LOS) significantly for infants with moderate to severe bronchiolitis, without apparent adverse effects[30].

A Cochrane systematic review published in 2013 included 11 trials of 3% saline compared with NS, 6 of which examined length of hospital stay (LOS). The meta-analysis found that nebulized HTS decreased LOS in infants with bronchiolitis by 1.15 days[34].

Due to the efficacy and cost-effectiveness of the treatment, nebulizedHS should be considered in clinical practice for the treatment of acute bronchiolitis in infants. Further randomized controlled trials (RCT)s are warranted to address the optimal treatment regimen of nebulized HS in infants with acute bronchiolitis[32].

Inpatients and outpatients (but not those patients in the ED setting) treated with nebulized 3% saline, compared to those treated with nebulized 0.9% saline, had a significantly shorter mean hospital LOS-primary outcome and lower post-inhalation clinical score during the first 3 days of treatment[10].

Mist-steam and chest physiotherapy: Mist-steam and chest physiotherapy appear to have no role in treating bronchiolitis[3]. Roque´ I Figuls et al. determined the efficacy of chest physiotherapy (CPT) in infants (<24 months of age) as a main objective, and the efficacy of different techniques of CPT (i.e., vibration & percussion and passive forced exhalation) as secondary objective[36]. Nine RCTs were included, comparing CPT vs. no intervention; five trials evaluated vibration & percussion techniques and four trials evaluated passive expiratory techniques. No significant differences in the severity of diseases were observed and results were negative for both types of CPT.

Nutrition and hydration: Fluid administration is an important intervention in children with bronchiolitis, whose ability to feed properly is impaired by fever, tachypnea, moderate or severe respiratory distress, bouts of cough and upper respiratory secretions. For mild cases, feeding more frequently in smaller amounts is better tolerated and breastfeeding should not be suspended. For moderate and severe cases, nutrition and hydration can be maintained either by intravenous fluid administration or by nasogastric tube feeding[37].These two approaches have no significant differences in terms of the length of hospital stay or transfers to intensive care, but the nasogastric tube is easier to insert[38]. Nasogastric feeding has also proved to be safe[3].

Surfactant: Exogenous surfactant administration appears to favorably change the hemodynamics of the lungs and may be a potentially promising therapy for severe bronchiolitis. Administration of exogenous surfactant among children may decrease the duration of mechanical ventilation and duration of ICU stay and had favorable effects on oxygenation and CO_2 elimination at 24 hours[39].

General prevention: It is important not to forget that, although RSV accounts for the majority of cases, it is not the only virus implicated in bronchiolitis. General preventive majors are essential to reduce the

incidence of acute bronchiolitis. Health education to the parents & the caregivers is still an important intervention for general prevention. Frequently washing hands and stethoscopes, and decontamination with alcoholic solutions, cleaning firm surfaces with water and disinfectant, and avoiding any sharing of contaminated objects[7], avoidance of exposing children to passive smoking[40], and breastfeeding have proved very effective for protecting the infants and children against lower respiratory tract infections & in particular the RSVinfection[41]. Use of gloves, aprons or gowns (during direct contact with the patients), isolation of the confirmed cases are also the important preventive measures for RSV infection[42].

DISCUSSION

The American Academy of Pediatrics (AAP) recommended in their evidence-based practice management guideline (published in 2006) that inhaled bronchodilators can be only used when there is a positive documented clinical response. They also recommended that corticosteroid should not be used routinely and antibiotics can be used in case of a coexisting bacterial infection[43]. Recently, two studies designed to determine the impact of this AAP guideline were published. In the post-guidelines period, fewer children received a trial of racemic epinephrine or albuterol, physicians more often discontinued albuterol when it was documented as ineffective, and the use of corticosteroid in children without a history of reactive airway disease or asthma dropped[44].

The review of 20 SRCTs, (up to June 2014) showed that only epinephrine (for outpatients), nebulized 3% saline (for inpatients) and exogenous surfactant (small trials in ventilated children) had some small benefit mainly in short-term outcomes as was described previously[10].

The American Academy of Pediatrics (AAP) guideline 2014 recommended administering nebulized hypertonic saline only for inpatients but not to administer salbutamol, epinephrine or systemic corticosteroids for infants and children with bronchiolitis[45].

CONCLUSION

The most suitable treatment for bronchiolitis is still debated. CPG shows improved results which consist of supportive therapy but still there is lacking on its implementation and the commitment from the provider.

REFERENCES

1. American Academy of Paediatrics. Subcommittee on Diadnosis and Management of Bronchiolitis. Paediatrics 2006: 118:1774-93.
2. Vicencio AG. Susceptibility of Bronchiolitis in infants. Curr Opin Paediatr 2010:22:302-6.
3. Liviana Da Dalt, Silvia Bressan, Francesco Martinolli, et al. Treatment of bronchiolitis: state of the art. Early Human Development 2013:89(S1): S31-S36.
4. Haas Lee, Thijsen SF, van Elden L, et al. Human metapnemoviruses in adults.Viruses 2013: Jan 8: 5(1): 87-110.
5. Dora Zamora-Flores, DNP, RN, CPNP, Nancy H. Busen, PhD, RN, FNP-BC & et al. Implementing a Clinical Practice Guideline for the Treatment of Bronchiolitis in a High-Risk Hispanic Pediatric Population. Journal of paediatric Health care 2015: 29(2):169–180
6. Nagakumar P, Doull I. Current therapy for bronchiolitis. Arch Dis Child 2012: 97(9):827–30.
7. Eugenio Baraldi , Dania El Mazloum, Michela Maretti, Francesca Tirelli, Laura Moschino , Bronchiolitis: update on the management.Early Human Development 2013:89(S4):S94–S95.
8. Wohl ME, Chernick V. State of the art: bronchiolitis. Am Rev Respir Dis 1978;118:, 759–81
9. Blom DJ, Ermers M, Bont L, van Woensel JB, et al. Inhaled corticosteroids during acute bronchiolitis in the prevention of post-bronchiolitis wheezing. Cochrane Database Syst Rev Jan 19, 2011;1: CD004881.
10. Jose A. Castro-Rodriguez, Carlos E. Rodriguez-Martinez, et al. Principal findings of systematic reviews for the management of acute bronchiolitis in children. Paediatric respiratory reviews: Jan 2015;volume 16 (4):267-75.
11. Fernandes RM, Bialy LM, Vandermeer B, et al. Gluco-corticoids for acute viral bronchiolitis in infants and young children. Cochrane Database of Systematic Reviews 2013; (Issue 6). http://dx.doi.org/10.1002/14651858.CD004878.pub4. Art. No.: CD004878.
12. Hartling L, Fernandes RM, Bialy L, Milne A, Johnson D, Plint A, et al. Steroids and, bronchodilators for acute bronchiolitis in the first two years of life: systematic review and meta-analysis. BMJ 2011;342:d1714
13. Plint AC, Johnson DW, Patel H, Wiebe N, Correll R, Brant R, et al. Epinephrine and dexamethasone in children with bronchiolitis. *N Engl J Med*. 2009: 360(20):2079-89.
14. Gadomski AM, Scribani MB. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev. 2014:6:CD001266.
15. Clavenna A, Sequi M, Cartabia M, et al. Effectiveness of nebulized beclomethasone in preventing viral wheezing: an RCT. Pediatrics. 2014 Mar;133(3):e505-12.
16. Gadomski AM, Lichenstein R, Horton L, King J, Keane V, Permutt T. Efficacy of albuterol in the management of bronchiolitis. Pediatrics 1994; 9:907e12.
17. Chevallier B, Aegerter P, Parat S, Bidat E, Renaud C, Lagardere B. Comparative study of nebulized salbutamol against placebo in the acute phase of bronchiolitis in 33 infants aged 1e6 months. Arch Pediatr 1995;2:11e7
18. Gadomski AM, Brower M. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev 2010;(12):CD001266
19. Gadomski AM, Bhasale AL. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev 2006;3:CD001266
20. Spurling GK, Doust J, Del Mar CB, Eriksson L. Antibiotics for bronchiolitis in children. Cochrane Database Syst Rev. 2011:(6):CD005189. doi: 10.1002/14651858.CD005189.pub3.
21. Ramesh P, Samuels M. Are methylxanthines effective in preventing or reducing apnoeic spells in infants with bronchiolitis? Arch Dis Child 2005;90: 321–2.

22. Ventre K, Randolph AG. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. *Cochrane Database Syst Rev*. 2007 Jan 24. CD000181. .
23. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. Pediatrics 1998;102 (3 Pt 1):531–7.
24. Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, Top Jr FH, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 2003;143 (4):532–40.
25. Harkensee C, Brodlie M, Embleton ND, Mckean M. Passive immunisation ofpreterm infants with palivizumab against RSV infection. J Infect 2006; 52 (1): 2–8.
26. American Academy of Pediatrics. Respiratory syncytial virus. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, editors. Red Book: 2012 Report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics; 2012, pp. 609–18.
27. McKiernan C, Chua LC, Visintainer PF, Allen H. High flow nasal cannula therapy in infants with bronchiolitis. J Pediatr 2010; 156:634–8.
28. Schibler A, Pham TM, Dunster KR, Foster K, Barlow A, Gibbons K, et al. Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery. Intensive Care Med 2011; 37:847–52.
29. Hilliard TN, Archer N, Laura H, Heraghty J, Cottis H, Mills K, et al. Pilot study of vapotherm oxygen delivery in moderately severe bronchiolitis. Arch Dis Child; 2012; 97:182–3.
30. Nicolai A, Ferrara M, Schiavariello C, Gentile F, Grande M E, Alessandroni C, Midulla S F. Viral bronchiolitis in children: A common condition with few therapeutic options. Early human development; 2013 Oct; 89 (3) :S7-11.
31. Luo Z, Fu Z, Liu E, Xu X, Fu X, Peng D, Liu Y, Li S, Zeng F, Yang X. Nebulized hypertonic saline treatment in hospitalized children with moderate to severe viral bronchiolitis. Clinical microbial infection. 2011Dec17(12):1829-33
32. Zhang L, Mendoza-Sassi RA, Klassen TP, Wainwright C.Nebulized Hypertonic Saline for Acute Bronchiolitis: A Systematic Review Paediatrics. 2015 Oct 136(4):687-701.
33. Yen-Ju Chen†, Wen-Li Lee†, Chuang-Ming Wang, Hsin-Hsu Chou. Nebulized Hypertonic Saline Treatment Reduces Both Rate and Duration of Hospitalization for Acute Bronchiolitis in Infants: An Updated Meta-analysis. Paediatrics & Neonatology; December 2014, Pages 431–438
34. Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulized hypertonic saline solution for acute bronchiolitis in infants. Cochrane database systematic review; 2013 Jul 31;7:CD006458
35. Linjie Zhang, MD, PhD , Raúl A. Mendoza-Sassi, MD, PhD , Terry P. Klassen, MD , Claire Wainwright, MD. Nebulized Hypertonic Saline for Acute Bronchiolitis: A Systematic Review. Paediatrics; 2015 October; Volume 136 (4):687-701
36. Roqué I Figuls M, Giné-Garriga M, Granados Rugeles C, Perrotta C. Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. *Cochrane Database Syst Rev*. 2012 Feb 15. 2:CD004873.
37. Babl FE, Sheriff N, Neutze J, Borland M, Oakley E. Bronchiolitis management in pediatric emergency departments in Australia and New Zealand: a PREDICT study. Pediatr Emerg Care 2008;24(10):656–8.
38. Oakley E, Borland M, Neutze J, Acworth J, Krieser D, Dalziel S, et al. Nasogastric hydration versus intravenous hydration for infants with bronchiolitis: a randomised trial. Lancet Respir Med 2013;1(2):113–20.
39. Jat KR, Chawla D. Surfactant therapy for bronchiolitis in critically ill infants. Cochrane Database Syst Rev. 2015 Aug 24; 8:CD009194.
40. Kott KS1, Salt BH, McDonald RJ, Jhawar S, Bric JM, Joad JP. Effect of second hand cigarette smoke, RSV bronchiolitis and parental asthma on urinary cysteinyl LTE4. Paeditr pulmonol, 2008 Aug; 43(8):760-6. doi: 10.1002/ppul.20853.
41. Wright M, Piedimonte G. Respiratory syncytial virus prevention and therapy: past, present, and future. Paeditr pulmonol, 2011 Apr;46(4):324-47. doi: 10.1002/ppul.21377.
42. Bronchiolitis in children. Scottish Intercollegiate Guidelines Network-SING, 2006 Nov.
43. Ilke Ozahı Ipek a, Emek Uyur Yalcin b, Rabia Gonul Sezer b,*, Abdulkadir Bozaykut, The efficacy of nebulized salbutamol, hypertonic saline and salbutamol/hypertonic saline combination in moderate bronchiolitis.
44. McCulloh RJ, Smitherman SE, Koehn KL, Alverson BK. Assessing the impact of national guidelines on the management of children hospitalized for acute bronchiolitis. Pediatr Pulmonol 2014;49:688–94.
45. Ralston SL, Lieberthal AS, Meissner HC, Alverson BK, Baley JE, Gadomski AM, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. Pediatrics 2014;135:e1474–502.