



Evidence based management of acute bronchiolitis

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Bronchiolitis is a common acute lower respiratory tract disease affecting infants. It is associated with viral infection and respiratory syncytial virus is the most frequently identified microorganism. Bronchiolitis remains one of the major reason for hospitalisation in children younger than 1-year. Its presentation is characterised by fever, coryza, cough, expiratory wheezing and distress. There were numerous clinical studies published on the efficacy of various medications used in managing this disease. However, the results of many of these studies were conflicting. Hence, controversies still exist concerning the pharmacological treatment of bronchiolitis. In this article, the current evidence from the recently published literature on different drugs given for acute bronchiolitis will be discussed. These include salbutamol, ipratropium bromide, epinephrine, steroid, ribavirin and montelukast.

Bronchodilator

There were four meta-analyses and one systemic review investigating the efficacy of bronchodilators in treating bronchiolitis. Salbutamol was the most frequently used bronchodilator among the clinical studies. Kellner et al found in his two meta-analyses that bronchodilator produced short term improvement in the clinical score.^{1,2} Its administration was not associated with any significant adverse effect. However, the magnitude of reduction in clinical score was small between the treatment and control group (pooled difference in clinical score -0.2; 95% CI -0.37 to -0.1). The clinical importance is therefore questionable. There was also no significant difference observed in the rate and duration of hospitalisation between both groups. For the remaining three studies, the authors did not find any evidence to suggest that use of salbutamol was associated with consistent clinical improvement in hospitalisation rate, physiological parameters or clinical scores.³⁻⁵ Thus,

routine use of salbutamol is not recommended judging from the available evidence.

As compared with salbutamol, ipratropium bromide is less controversial. No significant effect on the clinical outcomes was documented with ipratropium bromide in two systemic reviews by Schindler et al and King et al respectively.^{4,5} Therefore, use of ipratropium bromide in bronchiolitis is not advised.

Epinephrine

A recently published meta-analysis by Hartling et al investigated the efficacy of epinephrine in treating bronchiolitis.⁶ Fourteen randomised controlled trial were included of which they were further categorised into inpatient and outpatient studies for analysis. Clinical score was the only outcome found to be favouring epinephrine with the standardised mean difference (SMD) of -0.52 (CI -1.00, -0.03) among the inpatient studies comparing epinephrine and placebo. For the outpatient studies (3 trials), 5 outcomes including the clinical score at 60 minutes, change in oxygen saturation at 30 minutes, respiratory rate at 30 minutes and improvement favoured epinephrine. There was no significant difference in admission rate between the treatment and control group. The authors also compared the effect of epinephrine and salbutamol in both inpatient and outpatient studies. Respiratory rate at 30 minutes was the only outcome out of seven detected to be improved in the adrenaline group with weighted mean difference of -5.12 (95% CI -6.83, -3.41). Among the four outpatient studies, change in oxygen saturation at 60 minutes, heart rate at 90 minutes, respiratory rate at 60 minutes and "improvement" favoured epinephrine over salbutamol. The evidence is not sufficient to support use of epinephrine in the treatment of bronchiolitis among inpatients. There is some evidence to suggest the efficacy of epinephrine among outpatients but all the studies only investigated short term effect. A large and high quality trials is needed to substantiate the effect of epinephrine. Meanwhile, use of nebulised epinephrine should not be routinely recommended.

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Steroid

The trials for steroid in the management of acute bronchiolitis can be classified according to the types of patients involved in the studies namely inpatients, outpatients and intensive care patients.

A meta-analysis by Garrison et al concluded that systemic steroid was beneficial for treatment of bronchiolitis by demonstrating improvement in length of stay and duration of symptoms.⁷ However, five out of six included studies showed little or no beneficial effect and the actual benefit demonstrated was qualitatively small, i.e. less than half a day difference in hospitalisation. Hence, the result of this meta-analysis should be interpreted cautiously. In addition, two other inpatient trials published in recent few years failed to document any positive effect with the use of steroid.^{8,9} There is currently inadequate evidence to support routine use of steroid in hospitalised patients with bronchiolitis.

In contrast to the inpatient studies, three recently published trials performed in the emergency department have shown that systemic steroid was effective in reduction of clinical score, duration of symptoms and hospitalisation.¹⁰⁻¹² The corticosteroid used in the trials included 2 mg/kg of prednisolone for 3 to 5 days and one dose of 1 mg/kg of dexamethasone. Weinberger et al commented that the observed effect could have been explained by the early treatment provided in the emergency department when the inflammation of airway was still reversible.¹³ A large and well designed RCT is certainly required to confirm the efficacy on early initiation of steroid therapy. Though, the existing evidence may not be sufficient to recommend routine administration of steroid to patients with bronchiolitis in the outpatient setting, its use may be considered taking into account the results of these recent trials.

In the subgroup analysis of two separate studies by van Woensel et al, systemic steroid shortened the duration of mechanical ventilation, supplemental oxygen and hospital stay in bronchiolitis patients requiring mechanical ventilation.^{14,15} However, another trial performed on critical ill patients with bronchiolitis did not detect any significant difference in clinical outcomes of the steroid treated group.¹⁶ Further large scale trial is warranted to document the benefit of

steroid in managing severe bronchiolitis. Owing to the conflicting evidence, steroid should only be given to patients with severe bronchiolitis after careful consideration.

Ribavirin

A recent systemic review by King and his colleagues included 10 trials to investigate the effect of ribavirin for treatment of bronchiolitis.⁵ No significant difference on days of hospitalisation, length of time for intensive supportive interventions and duration of illness was detected. Three out of six trials reporting clinical score and symptoms as their outcome did not find any improvement after treatment with ribavirin. The results of the remaining three trials reporting positive effect were not entirely consistent. The authors therefore concluded that no evidence of ribavirin use led to consistent or more than transient improvements in clinical outcome.

In another systemic review published in Cochrane Library 2004, the investigators found reduction in mortality (OR 0.58; 95% CI 0.18 to 1.85), probability of respiratory deterioration (OR 0.37; 95% CI 0.12 to 1.18), days of hospitalisation (weight mean difference (WMD) of 1.9 days; 95% CI -4.6 to +0.9) and days of ventilation (WMD of 1.8 days; 95% CI -3.4 to -0.2) in infants and young children with respiratory syncytial virus infection of the lower respiratory tract with the use of ribavirin.¹⁷ However, the included trials were small and lacked sufficient power to provide reliable estimate of the effects. A large RCT on ribavirin treatment for severe bronchiolitis is indicated to further clarify its efficacy.

Montelukast

Bisgaard and his groups described their observation on the effect of montelukast on symptoms of RSV bronchiolitis.¹⁸ Infants were free of any symptoms on 22% of the days and nights after receiving 28 days of montelukast therapy whereas patients on placebo had 4% of symptom-free days and nights ($p=0.015$). Also, the day time cough was reduced and exacerbation was delayed significantly in the montelukast-treated group. However, this study was designed to evaluate the treatment effect on postbronchiolitis symptom and its role on acute symptom has not been addressed. To date, this study is the only trial reporting the use



of montelukast in the management of bronchiolitis. More studies are needed to determine the efficacy of montelukast on acute symptoms of bronchiolitis before any recommendation can be made on its use.

In summary, many studies identified for drugs given in bronchiolitis were underpowered and their results were not uncommonly conflicting. Large trials on individual medications are definitely indicated to provide clinicians with adequate guidance for an evidence based approach in management of this common disease of paediatric patients.

References

1. Kellner JD, Ohlsson A, Gadomski AM, Wang EE. Efficacy of bronchodilator therapy in bronchiolitis: a meta-analysis. *Arch Pediatr Adolesc Med* 1996;150:1166-72.
2. Kellner JD, Ohlsson A, Gadomski AM, Wang EE. Bronchodilators for bronchiolitis (Cochrane Review). In: *The Cochrane Library*, Issue 4 2002. Oxford: Update Software.
3. Flores G, Horwitz RI. Efficacy of beta 2 agonists in bronchiolitis: a reappraisal and meta-analysis. *Pediatrics* 1997;100(2 Pt 1):233-9.
4. Schindler M. Do bronchodilators have an effect on bronchiolitis? *Crit Care* 2002;6:111-2.
5. King VJ, Viswanathan M, Bordley WC, Jackman AM, Sutton SF, Lohr KN, et al. Pharmacologic treatment of bronchiolitis in infants and children: a systematic review. *Arch Pediatr Adolesc Med* 2004;158:127-37.
6. Hartling L. Epinephrine for bronchiolitis (Review). *The Cochrane Library*, Volume(2), 2004.
7. Garrison MM, Christakis DA, Harvey E, Cummings P, Davis RL. Systemic corticosteroids in infant bronchiolitis: a meta-analysis. *Pediatrics* 2000;105:E44.
8. Berger I, Argaman Z, Schwartz SB, Sagal E, Kiderman A, Branski D, et al. Efficacy of corticosteroids in acute bronchiolitis: short-term and long-term follow-up. *Pediatr Pulmonol* 1998;26:162-6.
9. Zhang L, Ferruzzi E, Bonfanti T, Auler MI, D'avila NE, Faria CS, et al. Long and short-term effect of prednisolone in hospitalized infants with acute bronchiolitis. *J Paediatr Child Health*; 2003;39:548-51.
10. Goebel J, Estrada B, Quinonez J, Nagji N, Sanford D, Boerth RC. Prednisolone plus albuterol versus albuterol alone in mild to moderate bronchiolitis. *Clin Pediatr (Phila)* 2000;39:213-20.
11. Schuh S, Coates AL, Binnie R, Allin T, Goia C, Corey M, et al. Efficacy of oral dexamethasone in outpatients with acute bronchiolitis. *J Pediatr* 2002;140:27-32.
12. Csonka P, Kaila M, Laippala P, Iso-Mustajarvi M, Vesikari T, Ashorn P. Oral prednisolone in the acute management of children age 6 to 35 months with viral respiratory infection-induced lower airway disease: a randomized, placebo-controlled trial. *J Pediatr* 2003;143:725-30.
13. Weinberger M. Corticosteroids for first-time young wheezers: current status of the controversy. *J Pediatr* 2003; 143:700-2.
14. van Woensel JB, Wolfs TF, van Aalderen WM, Brand PL, Kimpen JL. Randomised double blind placebo controlled trial of prednisolone in children admitted to hospital with respiratory syncytial virus bronchiolitis. *Thorax* 1997;52: 634-7.
15. van Woensel JB, van Aalderen WM, de Weerd W, Jansen NJ, van Gestel JP, Markhorst DG, et al. Dexamethasone for treatment of patients mechanically ventilated for lower respiratory tract infection caused by respiratory syncytial virus. *Thorax* 2003;58:383-7.
16. Buckingham SC, Jafri HS, Bush AJ, Carubelli CM, Sheeran P, Hardy RD, et al. A randomized, double-blind, placebo-controlled trial of dexamethasone in severe respiratory syncytial virus (RSV) infection: effects on RSV quantity and clinical outcome. *J Infect Dis* 2002;185:1222-8.
17. Ventre K, Randolph A. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. *Cochrane Database Syst Rev* 2004; CD000181.
18. Bisgaard H; Study Group on Montelukast and Respiratory Syncytial Virus. A randomized trial of montelukast in respiratory syncytial virus postbronchiolitis. *Am J Respir Crit Care Med* 2003;167:379-83.