

The evidence based Management of Bronchiolitis

H Ko, I Chu

Citation

H Ko, I Chu. *The evidence based Management of Bronchiolitis*. The Internet Journal of Pediatrics and Neonatology. 2008 Volume 10 Number 1.

Abstract

Acute bronchiolitis is a common respiratory illness in children under 12 months of age. Although much is known about the pathological features and manifestations of bronchiolitis, the optimal treatment for this condition is still unavailable. Various treatment modalities have been championed over the last few decades, with varying degree of success. The author has critically reviewed the most current literature on the effectiveness of some commonly used outpatient treatment modalities in the management of bronchiolitis.

INTRODUCTION

Bronchiolitis is one of the most common respiratory problems in the first year of life^[1]. It is an inflammation of the bronchioles and most cases are viral in origin. Infants usually present with fever, cough, tachypnoea, wheezing and increased mucous production. The predominant pathological features in acute bronchiolitis are inflammation of the respiratory and terminal bronchioles, the process includes edema, necrosis of epithelial cells, production of mucus and possibly some degree of bronchospasm^[2]. Although much is known about the mechanism and manifestation of bronchiolitis, the optimal treatment for this condition is still unavailable.

The treatment for acute bronchiolitis is mainly supportive, including supplemental oxygen, nasal washing, IV fluids, and mechanical ventilation when necessary. Many physicians use a combination of treatments, including bronchodilators, corticosteroid, hypertonic saline and anticholinergic agent, with varying degree of success. The rationale in favor of these treatments is the potential to reduce mucous production and increase secretion clearance. This paper will take an evidence based approach to the various treatment modalities used in acute bronchiolitis.

BRONCHODILATOR

There has been longstanding controversy about the effectiveness of bronchodilator for bronchiolitis and early work has led to conflicting results. A recent meta-analysis published by the Cochrane Collaboration included a total of 22 clinical trials studying 1428 infants with bronchiolitis^[3]. The overall clinical score improvement was statistically

significant (standardized mean difference (SMD) -0.48).

However, the authors questioned the clinical importance of such improvement, because the scoring systems used in these studies were quite different. There was no significant difference in the improvement of oxygenation (weighted mean difference (WMD) -0.57, 95% CI -1.17 to 0.03), the rate of hospitalization (18% in treatment group and 26% in control group) or duration of hospitalization (WMD 0.02 days, 95% CI -0.32 to 0.36).

This meta-analysis also reported adverse effects with the use of bronchodilators: tachycardia ($P < 0.05$), decreased oxygen saturation ($P < 0.05$), flushing, hyperactivity, tachycardia and prolonged cough and tremor.

SYSTEMATIC GLUCOCORTICOSTEROID

In some parts of the world, many physicians still use corticosteroid for the treatment of bronchiolitis^[2,3]. The rationale in favor of corticosteroid is the inflammatory changes in the bronchioles of patients with bronchiolitis, which is supported by the presence of inflammatory mediators in the bronchiole^[4].

The most recent systematic review on this topic was published in 2004 and included a total of 1,198 patients aged 0 to 30 months from thirteen randomised trials^[5]. These patients were treated with the equivalent of 0.5 to 10 mg/kg of systemic prednisone for two to seven days. The primary outcome of interest was length of hospital stay (LOS) in admitted infants and young children, which was reported in 10 trials. LOS in treated children was 0.38 days fewer than the placebo group (95% CI -0.81 to 0.05), indicating no

significant difference.

Other outcomes include day three clinical score, hospital admission rates, readmission rate, respiratory rate and hemoglobin oxygen saturation, none of which showed significant difference between the treatment and placebo groups.

HYPERTONIC SALINE

Many studies have shown hypertonic saline can improve muco-ciliary clearance in children with cystic fibrosis^[67]. In vivo, hypertonic saline inhalation increases the volume of airway surface liquid and increases rates of mucociliary clearance in normal subjects^[8].

A Cochrane review on the use of hypertonic saline in bronchiolitis was published in 2008^[8]. It included three inpatient trials with a total of 189 infants and found the use of nebulized 3% saline significantly shorten the length of hospital stay compared to those treated with nebulized 0.9% saline, with a mean difference of -0.94 days (P = 0.0006). This represents a 25.9% reduction from the mean length of hospital stay in the 0.9% saline group^[8].

Because the length of hospital stay can be affected by administrative and social factors unrelated to the clinical condition of a patient^[9], the author has assessed the discharge criteria for each study. Mandelberg et al ^[10]. and Tal et al ^[11] based their discharge decision on clinical grounds (such as discontinuation of supplemental oxygen, absence of chest recession, adequate feeding without the need for intravenous fluids) whereas Kuzik ^[12] used a protocol-defined discharge criteria (Respiratory Distress Assessment Instrument ^[13] score <4 and an O2 saturation at least 95% in room air for 4 hours)..

The pooled results of three trials demonstrate a statistically significant lower mean post-inhalation score among infants treated with 3% saline inhalation compared to those treated with 0.9% saline inhalation in the first two days of treatment. The mean difference was -0.75 (P = 0.02) for day 1, -1.18 (95% CI -1.97 to -0.39, P = 0.003) for day 2 and -1.28 (P = 0.05) for day 3.

The authors concluded that nebulized 3% saline may significantly reduce the length of hospital stay and improve the clinical severity score in infants with acute viral bronchiolitis.

ANTI-CHOLINERGIC AGENT

Anti-cholinergic agent is frequently prescribed in children with wheeze. However, its role in the management of bronchiolitis is uncertain. A Cochrane review examining the role of anti-cholinergic agent in children under the age of two years with wheeze was published in 2005^[14].

The literature search identified 6 trials for the analysis. Because the authors used “wheeze” as the unifying clinical sign defining the group of patients with wheezy bronchitis, bronchiolitis and asthma, the recruited trials included children with recurrent wheeze or first time wheeze.

The author has extrapolated data from Wang et al^[15] and Schuh et al^[16] because only these two trails included patients with first time wheeze. Wang et al compared ipratropium and placebo in 31 patients and reported no significant reduction in the duration of hospitalization, change in oxygen saturation at discharge or day 3, or change in symptom scores at discharge or day 3. Schuh et al compared ipratropium bromide plus B2 agonist and B2 agonist alone in 69 patients and reported no difference in the frequency of a perceived ‘excellent’ response, change in respiratory rate or improvement in oxygen saturation^[16].

The results reported here do not support the use of anti-cholinergic agent for first time wheezing infants.

DISCUSSION

The Cochrane review of trials in infants with bronchiolitis has found that bronchodilators produce a statistically significant improvement in average clinical score, but this may not be clinically important and is associated with increased costs and adverse effects. In addition, the authors questioned the validity of this result because studies included in this review use different scoring system and included patients with recurrent wheezing, usually due to asthma.

The Cochrane Review on hypertonic saline showed it not only reduces the duration of hospitalization but also improves symptom scores in acute bronchiolitis. 3% hypertonic saline is a relatively inexpensive treatment but the potential economic and social gain is enormous: earlier discharge means children return home early and their parents return to works sooner and lower hospital costs^[10].

The precise mechanism of hypertonic saline in bronchiolitis has not been studied but extensive works have been done in normal subjects and patients with cystic fibrosis. Desgupta et

al demonstrated that hypertonic saline enhances mucociliary clearance in vivo and has a greater effect on mucous clarity than DNase in vitro^[17]. Hypertonic saline has a favorable effect on the mucous membrane and mucous transport in cystic fibrosis by the following mechanisms: 1) hypertonic saline induces an osmotic flow of water into mucus layer, rehydrates secretions, and improves mucus rheology^[18]; 2) hypertonic saline breaks the ionic bonds within the mucus gel, thereby reducing the degree of cross-links and entanglement and lowering the viscosity and elasticity^[19]. Hypertonic saline also stimulates cilia beat via the release of prostaglandin E2^[20] and decreases inflammatory response of polymorphonuclear leukocytes^[21].

The Cochrane review on corticosteroid found no significant difference in length of hospitalization and clinical score between the treatment and placebo groups. Many experts believed the use of corticosteroids would persist “unless a large sample trial of the most common interventions is mounted.”

A large sample sized, well thought-out study design and careful implemented randomized controlled trials on the use of corticosteroid in bronchiolitis was published in 2007^[22]. It recruited children with moderate to severe bronchiolitis from 20 emergency departments for a 3-year period. 600 children aged 2 to 12 months with a first episode of wheezing due to moderate to severe bronchiolitis (defined by means of a Respiratory Distress Assessment Instrument score > 6) were randomized to receive a single dose of oral dexamethasone (1mg/kg) or placebo. The results showed no significant difference in terms of hospital admission rate (39.7% for the dexamethasone group and 41% for the placebo group (P=0.74)). The mean 4-hour Respiratory Assessment Change Score was -5.3 for the dexamethasone group and -4.8 for the placebo group (P=0.21). Furthermore, the mean length of stay for hospitalized patients was 2.55 days in the dexamethasone group and 2.27 days in the placebo group (P=0.10).

Weinberger et al have hypothesized that the anti-inflammatory effects of steroid might only be useful in the early phases of acute viral bronchiolitis, before the inevitable widespread necrosis of the respiratory epithelium^[23]. This is an attractive hypothesis as parents usually seek medical attention when their infants and young children develop respiratory distress and wheezing, about 3 to 5 days after the onset of the illness. At this stage, the epithelial necrosis in bronchiolitis is likely to be present. However, this

hypothesis is difficult to test because most studies did not specify the onset of the illness.

The use of anti-cholinergic agents in patient with first time wheeze did not lead to any significant benefit when compared with placebo or B2 agonist^[1516]. However, the number of patients in these two trials is small. A large randomized controlled trial with carefully chosen outcome, is required to clarify the role of anti-cholinergic agent before any firm conclusion can be drawn.

CORRESPONDENCE TO

Dr. I-Wen Chu Department of Pediatrics Taichung Hospital, Department of Health, The Executive Yuan, No. 199, San Min Road, Sec. 1, Taichung City, Taiwan 403 Tel: (886)4-22294411 ext. 2672 Fax: (886)4-22296480 E-mail address: iwenchu@bigpond.com

References

1. Maayan C, Itzhaki T, Bar-Yishay E, Gross S, Tal A and Godfrey S. The functional response of infants with persistent wheezing to nebulized beclomethasone dipropionate. *Pediatr Pulmonol* 1986;2:9-14.
2. Calogero C and Sly PD. Acute Viral Bronchiolitis: To treat or not to treat- That is the question. *J of Pediatrics* 2007;151:235-237.
3. Khine H, Crain EF. Medication use in acute bronchiolitis: a survey of pediatric and adult emergency department physicians. *Arch Pediatr Adolesc Med* 1996;150:63(supp).
4. Klassen TP. Recent advances in the treatment of bronchiolitis and laryngitis. *Pediatric Clinics of North America*, 1997;44:249-261.
5. Patel H, Platt R, Lozano JM, Wang EEL. Glucocorticoids for acute viral bronchiolitis in infants and young children. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD004878. DOI: 10.1002/14651858.CD004878.
6. Bye PTP, Elkins MR. Mini-symposium: airway clearance in cystic fibrosis. Other mucoactive agents for cystic fibrosis. *Pediatr Respir Rev* 2007;8:30-9
7. Eng PA, Morton J, Doubllass JA, Riedler J, Wilson J, Robertson CF. Short-term efficacy of ultrasonically nebulized hypertonic saline in cystic fibrosis. *Pediatr Pulmonol* 1996;21:77-83.
8. Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulized hypertonic saline solution for acute bronchiolitis in infants. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No.: CD006458. DOI: 10.1002/14651858.CD006458. pub2.
9. Boogaard R, Hulsmann and van Veen L et al. Recombinant human deoxyribonuclease in infants with respiratory syncytial virus bronchiolitis. *Chest* 2007;131:
10. Mandelberg A, Tal G, Witzling M et al. Nebulized 3% hypertonic saline solution treatment in hospitalized infants with viral bronchiolitis. *Chest* 2003;123:481- 487.
11. Tal G, Cesar K, Oron A, Houris S, Ballin A and Mandelberg A. Hypertonic saline/Epinephrine treatment in hospitalized infants with viral bronchiolitis reduces hospitalization stay: 2 years experience. *IMAJ* 2006;8:169-173.
12. Kuzik BA, Qadhi SA, Kent S et al. Nebulized hypertonic saline in the treatment of viral bronchiolitis in infants. *J*

Pediatr 2007;151:266-70.

13. Lowell DI, Lister G and Von Koss H et al. Wheezing in infants: the response to epinephrine. *Pediatrics* 1987;79:939-45.

14. Everard ML, Bara A, Kurian M, N'Diaye TM, Ducharme F, Mayowe V. Anticholinergic drugs for wheeze in children under the age of two years. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD001279. DOI: 10.1002/14651858.CD001279.pub2.

15. Wang EE, Milner R, Allen U, Maj H. Bronchodilators for treatment of mild bronchiolitis: a factorial randomised trial. *Archives of Disease in Childhood* 1992;67(3):289-93.

16. Schuh S, Johnson D, Canny G, Reisman J, Shields M, Kovesi T, et al. Efficacy of adding nebulized ipratropium bromide to nebulized albuterol therapy in acute bronchiolitis. *Pediatrics* 1992;90(6):920-3.

17. Dasgupta B, Tomkiewicz RP, Boyd WA et al. Effects of combined treatment with rhDNase and airflow oscillations on spinnability of cystic fibrosis sputum in vitro. *Pediatr Pulmonol* 1995;20:78-82.

18. Robinson M, Hemming AL, REgnis JA et al. Effect of increasing doses of hypertonic saline on mucociliary clearance in patients with cystic fibrosis. *Thorax* 1997;52:900-903.

19. Wark PAB, McDonald V, Jones AP. Nebulised hypertonic saline for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD001506. DOI:10.1002/14651858.CD001506.pub2.

20. Assouline G, Leibson V, Danon A. Stimulation of prostaglandin output from rat stomach by hypertonic solution. *European Journal of Pharmacology* 1977;44:271-3.

21. Ciesla DJ, Moore EE, Zalen G et al. Hypertonic saline attenuation of polymorphonuclear neutrophil cytotoxicity: timing is everything. *J Trauma* 2000;48:388-95.

22. Corneli HM, Zorc JJ, Majahan P et al. A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *N Engl J Med* 2007;357:331-9.

23. Weinberger M. Corticosteroids for first-time young wheezers: current status of the controversy. *Journal of Pediatrics* 2003;143:700-1.

Author Information

Hui-Ming Ko, MD

Department of Pediatrics, Cheng Ching Hospital

I-Wen Chu, MBBS

Department of Pediatrics, Taichung Hospital