Respiratory Medicine (2000) **94,** 709–714
doi:10.1053/rmed.2000.0807, available online at http://www.idealibrary.com on IDEAL®

Inhaled nebulized adrenaline improves lung function in infants with acute bronchiolitis

K. C. Lødrup Carlsen* and K.-H. Carlsen†

*Department of Paediatrics, Section of Allergology and Pulmonology, Woman Child Clinic, Ullevål Hospital, N-0407 Oslo, and †Voksentoppen Center of Asthma, Allergy and Chronic lung diseases in Children, Ullveien 14, N-0791 Oslo, Norway

β_2-agonists have questionable symptomatic effect in infants with acute bronchiolitis, whereas inhaled, nebulized racemic adrenaline, commonly used in Norway, appears (clinically) to be effective. Limited lung function observations during acute bronchiolitis exists, and less for assessing possible effects inhaled adrenaline.

In this preliminary study, tidal flow-volume loops were measured in 16 infants with acute bronchiolitis and seven healthy controls (mean age 7·9 and 4·4 months, respectively), with repeated measurements 15 min after inhaled nebulized racemic adrenaline (4 mg diluted in 2 ml saline) in nine bronchiolitis patients.

The ratio of time to reach peak tidal expiratory flow to total expiratory time (t_{PTEF}/t_E) was significantly reduced in children with acute bronchiolitis (mean, 95% CI) (0·08, 0·05–0·10) compared to controls (0·31, 0·18–0·43), with significant improvement after inhaled racemic adrenaline 0·19 (0·13–0·25), parallel with significant clinical improvement.

Lung function (t_{PTEF}/t_E) was reduced in infants with acute bronchiolitis and improved significantly after inhaled racemic adrenaline. Inhaled racemic adrenaline is potentially an important alternative for treating infants with acute bronchiolitis.

Key words: tidal flow volume loops; lung function; bronchiolitis; racemic adrenaline; nebulized.

Respir. Med. (2000) **94,** 709–714

Introduction

Medication available for the symptomatic treatment of bronchiolitis in infants and very young children is often of limited value. The main treatment of acute bronchial obstruction (BO) in infants and toddlers with bronchiolitis has been the administration of β_2-agonists, theophyllines and anti-cholinergic drugs.

The effect of β_2-agonist administrated orally, by inhalation or intravenously in infants with acute bronchiolitis is not clear. Some studies have reported efficacy of nebulized salbutamol (1–3), others found little or no effect in the youngest children (4–8) and some even demonstrated a paradoxical fall in oxygen saturation after salbutamol administration in infants with bronchiolitis (4,7,9). In Norway, inhaled nebulized racemic adrenaline has been used as the main symptomatic treatment in young children and infants with bronchiolitis for many years. Empirically this treatment has been effective in reducing the symptoms of BO, and recent studies support this (10–13).

Measures of lung function to assess possible effects of treatment in very young children are limited in general, and specifically with treatment of acute respiratory diseases. They are difficult to obtain during acute illness partly due to distress of the baby, but also as sedation is generally required for most types of measurements. However, in sedated babies (during their first 3 days in hospital) with bronchiolitis Sanchez *et al.* demonstrated a superior effect upon pulmonary mechanics of nebulized epinephrine compared to salbutamol (13). Henderson *et al.*, on the other hand, found no improvement in lung function by nebulized epinephrine in asymptomatic infants with recurrent wheeze (14).

The present study was thus performed to assess by tidal breathing parameters possible beneficial effect of inhaled racemic adrenaline in babies with acute bronchiolitis.

Received 31 January 2000 and accepted in revised from 7 February 2000.

Correspondence should be addressed to: Karin C. Lødrup Carlsen, Section of Allergology and Pulmonology, Department of Paediatrics, Woman Child Clinic, Ullevål Hospital, N-0407 Oslo, Norway. Fax: +47 22 11 86 6; E-mail: karinloedrup.carlsen@ulleval.no

Methods

STUDY DESIGN

Nebulized racemic adrenaline was given openly to children with acute bronchiolitis (as defined by Court) (15).

0954-6111/00/070709+06 $35·00/0

Patients were recruited consecutively as they presented to the outpatient or inpatient clinic, and were included after informed consent was given by their parents. Exclusion criteria were patients with so severe bronchiolitis that immediate treatment was required, a history of recurrent wheeze or present or past history of atopic dermatitis.

Measurements of tidal flow-volume (TFV) loops as well as clinical assessment (10) were performed before, and approximately 15 min after inhalation of racemic adrenaline. All measurements were performed with the patients awake, resting in their parents lap. The study was approved by the regional ethics committee.

Additionally, seven of the patients eventually participated in another ongoing study [The 'Environment and Childhood Asthma' Study (16)], where healthy controls were included for lung function measurements. However, these children did not receive racemic adrenaline, and only baseline lung function measurements are used in the present study for comparison.

SUBJECTS

Sixteen children (14 boys) with acute bronchiolitis, and seven healthy controls (four girls) were included into the present study. Characteristics of the children are given in Table 1. Nasal swabs for virus detection was not performed routinely, but respiratory syncytial virus (RSV) was detected in three of the patients. One child only presented with the second doctor-documented BO, but RSV was detected from nasal swabs in this patient. Apart for one child (who received racemic adrenaline 3·5 h prior to measurement, at the local doctor's surgery), none of the children had received any α- or β-stimulating medication on the day of testing prior to measurements. None of the patients received any regular treatment. At the time of the first measurement, all children with bronchiolitis had moderately severe BO scored according to the scale of Aas (17), where P0 denotes no obstruction to P6 denoting severe, life-threatening BO.

LUNG FUNCTION AND CLINICAL MEASUREMENTS

Lung function measurements were performed with the SensorMedics 2600 system consisting of an IBM-PS2/50Z (80286) computer with an outboard microprocessor controlled (8085) analogue to digital conversion module (15 channels for conversion, multiplexed through three 14-bit D/As that perform digital offset, range and conversion).

Flow was measured using a triple screen pneumotachograf (4500 series, Hans Rudolph, Missouri, USA), with a flow range of 0–30 l min^{-1}. Differential pneumotach pressure and mouth pressure was measured with Validyne DP-250 transducers (commercial versions of the MP-45) at ± 2 cm H_2O and $\pm$ 100 cm H_2O, respectively. The pneumotach was fitted to a close-fitting mask covering nose and mouth, with an air inflated cuff of an appropriate size for each infant. Integration of flow to volume was carried out at a rate of 256 samples sec^{-1}, without any filtering of the raw signal.

Tidal flow-volume (TFV) loops were stored in groups of four, chosen as the most representative curves from tracings of established tidal breathing. Real time analysis of the recorded data was performed by the SensorMedics system, and the reported data were derived from the mean of these four loops, as was the case for the respiratory rate.

Measurements took approximately 1–5 min according to the co-operation of the child.

Obstructive score based upon clinical examination was assessed together with lung function measurements as soon as practically possible after admission to the hospital, before any medication was administered. Racemic adrenaline (20 mg/ml^{-1} 0·2 ml diluted in 2 ml saline was then administered to the patient by nebulization (Pari Standard).

STATISTICAL ANALYSES

Statistical analysis was carried out with the Number Cruncher statistical system, and results are reported as mean values with 95% CI (in parentheses) unless otherwise stated. Differences were tested by two-tailed Wilcoxon signed rank tests for matched pairs. Differences were considered statistically significant with P-values $<5\%$.

Results

The results of baseline TFV measurements are given in Table 2, for all children with bronchiolitis, as well as controls. Compared with controls, mean respiratory rate tended to be higher (NS) (52·7 *vs.* 48·7 breaths min^{-1}, respectively), and lung function parameters (such as t_{PTEF}/t_E:0·08 vs. 0·31, respectively) significantly reduced in children with acute bronchiolitis (Fig. 1).

TABLE 1. Age and weight in the 16 infants and toddlers with acute bronchiolitis and seven controls

	Bronchiolitis $n = 16$	Controls $n = 7$	All subjects $n = 23$	P-value
Age (months)	7·9 (5·9–9·9)	4·4 (2·8–6·0)	6·8 (5·3–8·4)	0·06
Weight (kg)	8·9 (7·8–10·0)	7·1 (5·7–8·6)	8·35 (7·45–9·25)	0·02

TABLE 2. Lung function results in 16 children with bronchiolitis (B) and seven controls (C), before and 15 min after inhaled, nebulized racemic adrenaline ($n = 9$)

	Repeated measurements ($n = 9$)				
	Pre-	Post-	Bronchiolitis $n = 16$	Controls ($n = 7$)	P-value pre *vs.* post/ B *vs.* C
Resp. rate	46·7 (39·4–54·0)	50·9 (42·6–59·2)	52·7 (45·7–59·7)	48·7 (31·2–66·2)	0·5/0·7
V_E kg^{-1} (ml)	6·9 (5·7–8·1)	8·26 (7·0–9·5)	6·4 (5·5–7·2)	8·7 (7·9–9·6)	$<0·001$/0·04
t_{PTEF} t_E	0·08 (0·04–0·12)	0·19 (0·13–0·25)	0·08 (0·05–0·10)	0·31 (0·18–0·43)	0·007/<0.001
TEFTEF25/PTEF	0·46 (0·38–0·54)	0·63 (0·52–0·74)	0·45 (0·40–0·51)	0·70 (0·55–0·85)	0·04/0·003
PTEF (ml se^{-1})	154·4 (112·5–196·2)	211·0 (144·7–277·3)	155·7 (123·6–187·7)	147·5 (98·4–196·6)	0·93/0·07
TEF50	107·4 (77·5–137·4)	191·1 (119·4–262·7)	100·6 (79·3–121·9)	131·0 (80·1–181·9)	0·003/0·32
P0-6	3·57 (2·67–4·47)	1·86 (0·87–2·85)			0·03/n.a.

n.a.: Not applicable.

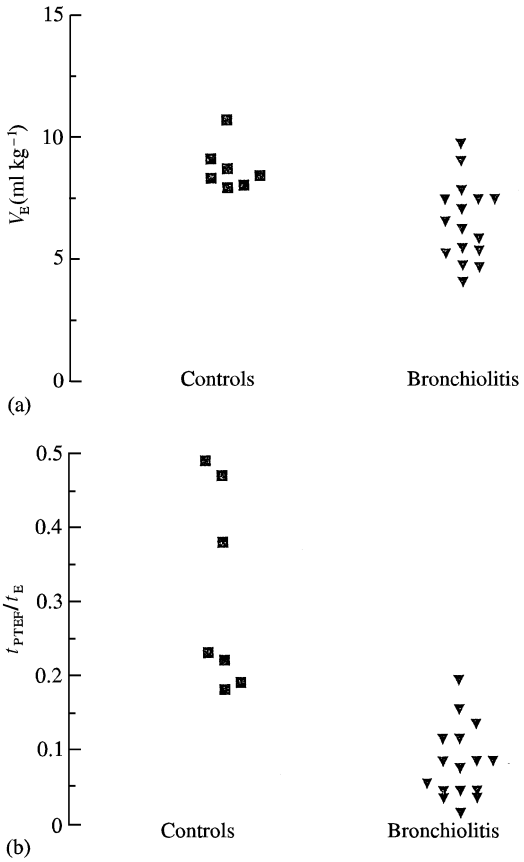

FIG. 1. Tidal breathing lung function parameters in 16 infants with acute bronchiolitis and seven healthy controls. (a) V_E (expiratory volume kg^{-1}) ($P<0·04$); (b) t_{PTEF}/t_E (ratio of time to peak expiratory flow to total expiratory time) ($P<0·0001$).

Clinical obstructive score fell significantly from before to after inhalation treatment.

Repeated studies of TFV-loops after inhaled racemic adrenaline were successful in nine children with acute bronchiolitis. The results of TFV measurements from before to after inhaled, nebulized racemic adrenaline are given in Table 2.

Tidal expiratory volume, t_{PTEF}/t_E (Fig. 2) and TEF25/PTEF as well as mid-tidal expiratory flow (TEF50) all improved significantly ($P<0·004$) from before to after nebulized racemic adrenaline.

In one infant taking part in a double-blind placebo controlled study (16) TFV loops were measured before any treatment, 15 and 30 min after receiving inhalation of what later was found to be placebo (with no clinical improvement) and subsequently after inhaled racemic adrenaline (openly given) (Fig. 3).

Discussion

Lung function, as measured by tidal flow volume loops was significantly reduced in infants with acute bronchiolitis, and improved significantly after inhaled, nebulized racemic adrenaline. The significantly reduced t_{PTEF}/t_E and TEF25/PTEF in infants with acute bronchiolitis are in accordance with reduced lung function during acute bronchiolitis in other studies (18–20). However, to our knowledge, TFV parameters obtained in infants with acute bronchiolitis have not previously been reported. One early (21) and several recent studies by Morris *et al.* (22–24) in adults, have demonstrated a clear association between decreased time ratio (corresponding to t_{PTEF}/t_E) and airway obstruction. Diminished tidal time or volume ratios have been reported even in asymptomatic subjects with obstructive airways disease (due to recurrent wheeze or asthma) (21,22,25–30), with a further reduction by provocation with histamine or metacholine (21,25,26,30). Thus, t_{PTEF}/t_E seems to be a reliable measure of airways obstruction (23,31). The mean baseline t_{PTEF}/t_E (0·08) in children with bronchiolitis reported in the present study was lower than the values generally reported in asymptomatic children (0·17–0·36) (25–28,30). This is to be

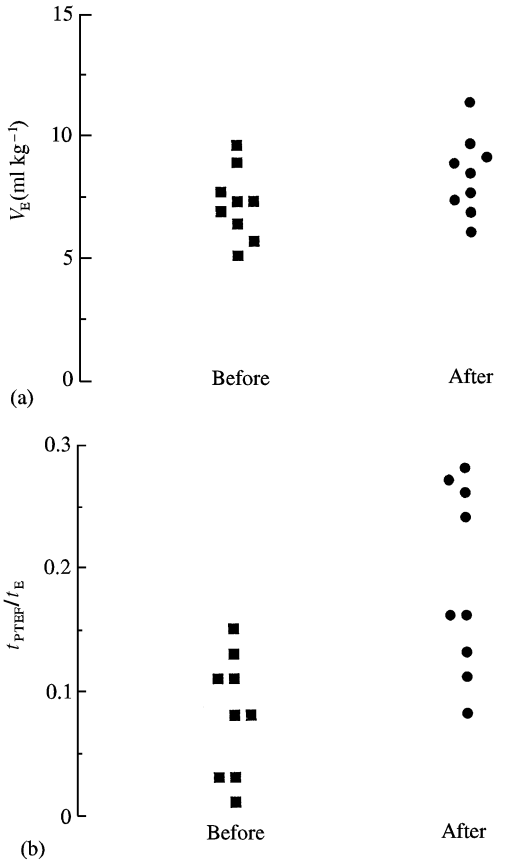

FIG. 2. Tidal breathing lung function parameters before and after inhalation of nebulized racemic adrenaline, in nine infants with acute bronchiolitis. (a) V_E (expiratory volume kg^{-1}) ($P<0{\cdot}001$), (b) t_{PTEF}/t_E (ratio of time to peak expiratory flow to total expiratory time) ($P<0{\cdot}001$).

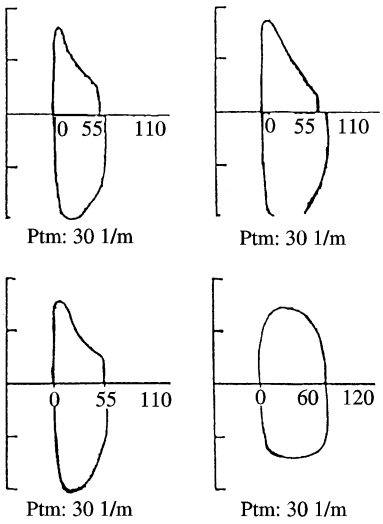

FIG. 3. Tidal flow volume loops in one 7-month-old boy with acute bronchiolitis. The baseline curve (top left) was measured during clinically moderately severe bronchial obstruction (BO). Curves (top right) and (bottom left) were measured after inhalation of what later was shown to be placebo, with no change in clinical condition. Curve (top right) was measured 15 min after openly given nebulized racemic adrenaline, with a concomitant attenuation of clinical BO.

expected, as all the patients had moderate airways obstruction during measurements.

The significant improvements in t_{PTEF}/t_E and TEF25/PTEF observed after inhalation of racemic adrenaline are in accordance with several recent placebo controlled studies in acute bronchiolitis, reporting improved clinical outcomes (10–12), as well as lung mechanics (13) after nebulized adrenaline. Improved tidal breathing parameters after inhaled β_2-agonists (salbutamol) have been demonstrated in asymptomatic infants and young children with obstructive airways disease (other than bronchiolitis) (27,28,31,32). However, one study found no effect on lung function (partial forced expiratory flow volume loops and airway conductance) of nebulized adrenaline in asymptomatic infants younger than 18 months (14). In acute bronchiolitis, it is possible that airway oedema plays an important role, whereas the contribution of bronchial muscle constriction may be relatively less important than is the case in acute asthma. The combined $\alpha-$ and β-receptor agonist racemic adrenaline is believed to affect both vascular as well as bronchial muscle, with a subsequent relief of BO. However, in contrast to β-receptor agonists, if the relief of BO by racemic adrenaline is primarily due to the effects upon airway wall oedema, any major effect on the airways in the absence of symptoms would be unlikely.

Although the present study was not placebo-controlled, two of the patients (Fig. 3 demonstrating TFV loops in one) took part in a double-blind, placebo-controlled study which demonstrated a significant improvement in clinical outcome after nebulized racemic adrenaline (10). However, it was difficult to establish an appropriately quiet setting to obtain TFV loops whilst attaching various equipment (including blood pressure monitor) for the reported placebo-controlled study, thus the present study focused upon objectively measured TFV loops.

The present study is small, observational and with no placebo group. However, even with successful repeated measurements in only 9/17 children with acute bronchiolitis, the difference in t_{PTEF}/t_E was highly significant, with a power of 93% to detect differences (two-sided), with a significance level of 0·05. The improved lung function was paralleled by improvement in clinical parameters, which is supported by previous reports of inhaled nebulised adrenaline being superior to β_2-agonist in relieving symptoms of acute bronchiolitis (12,13). Furthermore, previous reversibility studies from our laboratory have demonstrated no (or paradoxical) effect upon TFV loops by β_2-agonists in healthy infants, but significant improvement in asymptomatic young children with obstructive airways disease.

In conclusion, lung function measured by TFV loops was reduced in awake infants with acute bronchiolitis, and improved after inhaled nebulized racemic adrenaline. Although the study was only preliminary, our results

indicate that inhaled racemic adrenaline may be effective in relieving symptoms in children with acute bronchiolitis who in other countries are mainly treated with β_2-agonists of questionable effect (6,7,33,34). Further placebo-controlled studies are warranted as these results, if solidly confirmed may have a great impact upon general treatment guidelines for this disease.

References

1. Can D, Inan G, Yendur G, Oral R, Gunay I. Salbutamol or mist in acute bronchiolitis. *Acta Paediatr Jpn* 1998; **40:** 252–255.
2. Chevallier B, Aegerter P, Parat S, Bidat E, Renaud C, Lagardere B. Comparative study of nebulized sambutol against placebo in the acute phase of bronchiolitis in 33 infants aged 1 to 6 months. *Arch Pediatr* 1995; **2:** 11–17.
3. Klassen TP, Rowe PC, Sutcliffe T, Ropp LJ, McDowell IW, Li MM. Randomized trial of salbutamol in acute bronchiolitis. *J Pediatr* 1991; **118:** 807–811.
4. Prendiville A, Rose A, Maxwell DI, Silverman M. Hypoxaemia in wheezy infants after bronchodilator treatment. *Arch Dis Child* 1987; **62:** 997–1000.
5. Cengizlier R, Saraclar Y, Adalioglu G, Tuncer A. Effect of oral and inhaled salbutamol in infants with bronchiolitis. *Acta Paediatr Jpn* 1997; **39:** 61–63.
6. Goh A, Chay OM, Foo AL, Ong EK. Efficacy of bronchodilators in the treatment of bronchiolitis. *Singapore Med J* 1997; **38:** 326–328.
7. Ho L, Collis G, Landau LI, Le Souef PN. Effect of salbutamol on oxygen saturation in bronchiolitis. *Arch Dis Child* 1991; **66:** 1061–1064.
8. Sly PD, Lanteri CJ, Raven JM. Do wheezy infants recovering from bronchiolitis respond to inhaled salbutamol? *Pediatr Pulmonol* 1991; **10:** 36–39.
9. O'Callaghan C, Milner AD, Swabrick A. Paradoxical deterioration in lung function after nebulised salbutamol in wheezy infants. *Lancet* 1986; **2:** 1424–1425.
10. Kristjansson S, Lodrup Carlsen KC, Wennergren G, Strannegard IL, Carlsen KH. Nebulised racemic adrenaline in the treatment of acute bronchiolitis in infants and toddlers. *Arch Dis Child* 1993; **69:** 650–654.
11. Menon K, Sutcliffe T, Klassen TP. A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. *J Pediatr* 1995; **126:** 1004–1007.
12. Reijonen T, Korppi M, Pitkakangas S, Tenhola S, Remes K. The clinical efficacy of nebulized racemic epinephrine and albuterol in acute bronchiolitis. *Arch Pediatr Adolesc Med* 1995; **149:** 686–692.
13. Sanchez I, De Koster J, Powell RE, Wolstein R, Chernick V. Effect of racemic epinephrine and salbutamol on clinical score and pulmonary mechanics in infants with bronchiolitis. *J Pediatr* 1993; **122:** 145–151.
14. Henderson AJ, Arnott J, Young S, Warshawski T, Landau LI, LeSouef PN. The effect of inhaled adrenaline on lung function of recurrently wheezy infants less than 18 months old. *Pediatr Pulmonol* 1995; **20:** 9–15.
15. Court S. The definition of acute respiratory illness in children. *Postgrad Med* 1973; **49:** 771–776.
16. Lødrup Carlsen K.C. Tidal breathing analysis in infants and preschool children: tidal flow-volume loops. *Eur Respir Mon* 1997; **5:** 27–57.
17. Aas K. Heterogeneity of childhood asthma. *Allergy* 1981; **36:** 3–14.
18. Hughes DM, LeSouef PN, Landau LI. Effect of salbutamol on respiratory mechanics in bronchiolitis. *Pediatr Res* 1987; **22:** 83–86.
19. Soto ME, Sly PD, Uren E, Taussig LM, Landau LI. Bronchodilator response during acute viral bronchiolitis in infancy. *Pediatr Pulmonol* 1985; **1:** 85–90.
20. Springer C, Bar-Yishay E, Uwayyed K, Avital A, Vilozni D, Godfrey S. Corticosteroids do not affect the clinical or physiological status of infants with bronchiolitis. *Pediatr Pulmonol* 1990; **9:** 181–185.
21. Morris MJ, Lane DJ. Tidal expiratory flow patterns in airflow obstruction. *Thorax* 1981; **36:** 135–142.
22. Morris MJ, Madgwick RG, Lane DJ. Analysis of tidal expiratory flow pattern in the assessment of histamine-induced bronchoconstriction. Analysis of tidal expiratory flow pattern in the assessment of histamine-induced bronchoconstriction. *Thorax* 1995; **50:** 346–352.
23. Morris MJ, Madgwick RG, Collyer I, Denby F, Lane DJ. Analysis of expiratory tidal flow patterns as a diagnostic tool in airflow obstruction. *Eur Respir J* 1998; **12:** 1113–1117.
24. Williams EM, Madgwick RG, Morris MJ. Tidal expired airflow patterns in adults with airway obstruction. *Eur Respir J* 1998; **12:** 1118–1123.
25. Cutrera R, Filtchev SI, Merolla R, Willim G, Haluszka J. Analysis of expiratory pattern for monitoring bronchial obstruction in school-age children. *Pediatr Pulmonol* 1991; **10:** 6–10.
26. Benoist MR, Brouard JJ, Rufin P, Delacort C, Waernessyckle S, Scheinmann P. Ability of new lung function tests to assess metacholine-induced airway obstruction in infants. *Pediatr Pulmonol* 1994; **18:** 308–316.
27. Lødrup Carlsen KC, Halvorsen R, Ahlstedt S, Carlsen KH. Eosinophil cationic protein and tidal volume loops in children 0–2 years of age. *Eur Respir J* 1995; **8:** 1148–1154.
28. Carlsen KH, Lødrup Carlsen KC. Tidal breathing analysis and response to salbutamol in awake young children with and without asthma. *Eur Respir J* 1994; **7:** 2154–2159.
29. Dezateux CA, Stocks J, Dundas I, Jackson EA, Fletcher ME. The relationship between tPTEF:tE and specific airway conductance in infancy. *Pediatr Pulmonol* 1994; **18:** 299–307.
30. van der Ent CK, Brackel HJ, van der Laag J, Bogaard JM. Tidal breathing analysis as a measure of airway obstruction in children three years of age and older. *Am J Respir Crit Care Med* 1996; **153:** 1253–1258.

31. van der Ent CK, Brackel HJL, Mulder P, Bogaard JM, Brackel HJ. Improvement of tidal breathing analysis in children with asthma by on-line automatic data processing. *Eur Respir J* 1996; **9:** 1306–1313.
32. Chowdhury D, al Howasi M, Khalil M, Al-Frayh AS, Chowdhury S, Ramia S. The role of bronchodilators in the management of bronchiolitis: a clinical trial. *Ann Trop Paediatr* 1995; **15:** 77–84.
33. Dawson K. Rational prescribing for acute bronchiolitis. *Pharmacoeconomics* 1995; **8:** 9–13.
34. Flores G, Horwitz RI. Efficacy of β_2-agonists in bronchiolitis: a reappraisal and meta-analysis. *Pediatrics* 1997; **100:** 233–239.