

CHEST[®]

Official publication of the American College of Chest Physicians

ONLINE FIRST

This is an Online First, unedited version of this article. The final, edited version will appear in a numbered issue of *CHEST* and may contain substantive changes. We encourage readers to check back for the final article. Online First papers are indexed in PubMed and by search engines, but the information, including the final title and author list, may be updated on final publication.

<http://journal.publications.chestnet.org/>



Online First articles are not copyedited prior to posting.

©American College of Chest Physicians.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.

Word count: Abstract: 220 words; Text: 2431 words

Budesonide Nebulization Added to Systemic Prednisolone in The Treatment of Acute Asthma in Children: Double-Blind, Randomized, Controlled Trial

Running Title: Budesonide in Acute Asthma in Children

Abdullah A. Alangari^{1*}, MD; Nidal Malhis², MD; Mohamed Mubasher³, PhD; Najwa Al-Ghamedi⁴, PharmD; Mohamad Al-Tannir³, DMD; Muhammad Riaz³, MSc; Dale T. Umetsu⁵, MD, PhD; Saleh Al-Tamimi², MD

1. Department of Pediatrics, College of Medicine, King Saud University, Riyadh Saudi Arabia
2. Department of Emergency Medicine, King Fahad Medical City, Riyadh, Saudi Arabia
3. Research and Scientific Publication Centre, King Fahad Medical City, Riyadh, Saudi Arabia
4. Pharmacy Services Administration, King Fahad Medical City, Riyadh, Saudi Arabia
5. Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA

* Corresponding Author. E-mail: aangari@ksu.edu.sa. Department of Pediatrics, College of Medicine, King Saud University. P.O. Box 2925, Riyadh 11461, Saudi Arabia.

All authors declare no conflict of interest.

Funding: This study was supported by a grant from the Strategic Technologies Program of the National Plan for Science, Technology, and Innovation (NPSTI) in the Kingdom of Saudi Arabia. Grant number is 08-MED520-02.

An abstract of this study was presented in the World Allergy Organization (WAO) International Scientific Conference, 6-9 December 2012 in Hyderabad, India.

ABSTRACT

Background: Inhaled corticosteroids, known to be effective as a maintenance medication in chronic asthma, have also been suggested as a therapy for acute asthma, when given at high doses.

Methods: A double blind, randomized, placebo controlled trial was conducted in children 2-12 years of age with moderate or severe acute asthma, as determined based on 5-15 points clinical score, where 15 is the most severe. We compared the addition of budesonide 1500 mcg versus placebo to standard acute asthma treatment, which included salbutamol, ipratropium bromide and a single dose of prednisolone 2 mg/kg given at the beginning of therapy. The primary outcome was admission rate within 4 hours.

Results: A total of 906 emergency department visits of children with moderate or severe acute asthma were evaluated. Seventy-five cases out of 458 (16.4%) in the budesonide group versus 82/448 (18.3%) in the placebo group were admitted, (OR 0.84, 95% CI 0.58 to 1.23, p-value=0.38). However, among cases with high baseline clinical score (≥ 13), significantly fewer children were admitted in the budesonide group 27/76 (35.5%) than in the placebo group 39/73 (53.4%) (OR 0.42, 95% CI 0.19 to 0.94, p-value= 0.03).

Conclusion: The addition of budesonide nebulization did not decrease the admission rate of children with acute asthma overall. However, it may decrease the admission rate of children with severe acute asthma.

Trial registry: Clinicaltrials.gov; No.: NCT01524198; URL: www.clinicaltrials.gov

Abbreviation list:

ED: Emergency Department

ICS: Inhaled Corticosteroids

GLIMMIX: Generalized Linear Mixed Modeling

URI: Upper Respiratory Tract Infection

Key Words: admission rate, budesonide, emergencies, status asthmaticus.

INTRODUCTION

Asthma is the most common chronic disease of childhood (1, 2), and acute asthma is the most common pediatric emergency and reason for hospitalization. About 7-23% of patients with moderate or severe exacerbation are hospitalized (3-5). Current guidelines recommend that patients with moderate or severe asthma exacerbation receive 3 doses of inhaled or nebulized β -agonist in addition to ipratropium bromide every 15-20 minutes in the first hour (6-9). Systemic corticosteroids given early following presentation to the emergency department (ED) decrease the rate of admission especially in patients with more severe exacerbation (10).

Although several randomized controlled trials have shown clear efficacy of inhaled corticosteroids (ICS) in the management of acute asthma as compared to placebo (11, 12), only few studies have investigated the possibility of an added beneficial effect of ICS to systemic corticosteroids (13-16). Surprisingly, however, these pilot studies demonstrated that high dose nebulized budesonide, can acutely improve peak flow (15) and induce faster clinical improvement and hospital discharge (14, 17). Large adequately powered studies though, have not been performed, and a recent Cochrane systematic review of ICS use in acute asthma suggested further study in this area (11).

Here we hypothesize that adding high dose budesonide, 1500 mcg by nebulization to the standard asthma treatment of children in the ED during the first hour decreases their admission rate. Finding that the use of high dose inhaled budesonide indeed reduces hospitalization could lead to an important new treatment modality for acute asthma.

METHODS

Study design and participants

This was a double blind, randomized, two arm parallel groups, placebo controlled clinical trial to compare the efficacy of adding nebulized budesonide (1500 mcg) or placebo (normal saline) to the treatment of children with moderate or severe acute asthma. Enrolment continued from November 2010 through March 2012. Children were eligible if they were 2-12 years of age, with physician-diagnosed asthma or a previous episode of shortness of breath that responded to a β 2-agonist, and who presented to the ED with moderate or severe acute asthma exacerbation. Asthma severity was determined using a clinical scoring system adopted from Qureshi, et al (18) (Table 1). In this system, severe acute asthma was arbitrarily pre-defined as a score ≥ 12 and moderate asthma as a score 8-11. Children with either mild acute asthma or severe acute asthma in critical condition requiring non-standard immediate intervention were excluded. In addition, children with heart disease, chronic lung disease other than asthma, or those who had received systemic steroids within the past 7 days were also excluded. Patients were allowed to enroll in the study more than once. This study was conducted in accordance with the amended Declaration of Helsinki. The Institutional Review Board (IRB) at King Fahad Medical City in Riyadh, Saudi Arabia approved the protocol, and written informed consent was obtained from all patients' guardians (approval number 09-102).

Outcome measures and sample size determination

The study primary outcome measure was admission rate evaluated at 4 hours after administration of study assigned treatment. Secondary outcomes were change in asthma score and total length of stay in the ED.

Sample size was deemed sufficient to detect at least 12% differential between treatment groups in admission rate and a minimum of 90% statistical power with a two-sided 5% significance level. Additionally, sample size allowed for subgroup analysis using multiple comparisons criteria (19) to evaluate second order interactions. One to one treatment groups' allocation was pursued using a permuted block randomized scheme with variable block size.

Study interventions

Eligible children were randomized within the pharmacy to receive 3 doses of budesonide solution (500 mcg/dose) or placebo (normal saline). Patients also received β -agonist (2.5 mg salbutamol if patient weight <20 kg or 5 mg if ≥ 20 kg) and ipratropium 250 mcg per dose. The budesonide or normal saline were delivered from the pharmacy in opaque syringes and were not distinguishable from each other. Respiratory therapists, who were not involved in patients' recruitment or evaluation, mixed the delivered drug/placebo with salbutamol and ipratropium bromide. Normal saline was added to the treatment mixture to give a total volume of 3 mls per dose. They gave each patient one dose every 20 minutes, by jet nebulization over 1 hour using age appropriate facemask. Patients also received oral prednisolone 2 mg/kg with a maximum dose of 60 mg at the beginning of the study. All participating ED physicians underwent study protocol standardization and child enrolment training.

Assessment of children

All children were evaluated using the asthma scoring system (Table 1) at presentation (baseline), 1 and 2 hours from the start of medications. Patients who remained in the ED were also evaluated at 3 and 4 hours. A decision was made to admit or discharge

patients at 2, 3 or 4 hours. In order to be discharged, children must have had no accessory muscle use, wheezing is minimal or completely resolved, and O₂ saturation > 92%. Children who were not fit for discharge at 2 or 3 hour time points were either having severe symptoms and signs, and were admitted, or partially improved, and so received additional salbutamol nebulizations according to their symptoms severity or until they reached 4 hours time point. Discharged children were asked to continue prednisolone 2 mg/kg/day (maximum 60 mg) for 3 days in addition to β -agonist as needed and their usual maintenance medications. At 72 hours post-discharge, a follow-up phone call was conducted.

Statistical analysis

Univariate testing using Chi-square/Fisher Exact/Kruskal methods were adopted to compare groups in admission rate and ED stay time at 2, 3 or 4 hours, while t-test/Wilcoxon methods were used to compare changes in Asthma score. Multivariate statistical analysis plan allowed for the potential dependency in response due to reenrollments of a subset of children, using Generalized Linear Mixed Modeling (GLIMMIX) techniques in SAS software version 9.3 (Cary, NC) (20).

RESULTS

Description of study cohort

A total of 723 children were enrolled in the study, of whom 139 were allowed to re-enroll and be re-randomized (105 twice, 26 three times, 6 four times, and 2 children five times) to constitute 906 randomization assignments (458 in the budesonide group and 448 in the placebo group). Study enrolment details are displayed in Figure 1. At baseline, the overall mean $\pm$ SD asthma score was 10.63 ± 1.73 ; 30.9% had severe exacerbation; age: 5.52 ± 2.76 years; 35% girls; and 90% had prior physician diagnosed asthma.

Evaluation of randomization scheme and inter-rater reliability

Table 2 displays groups' baseline characteristics. The table indicates lack of any significant disparities between both groups. There was no difference in the baseline asthma score as well.

Inter-rater reliability of scoring the severity of acute asthma was assessed using intra-class correlation (ICC). The ratings of 3 randomly selected physicians, out of 15 different participating physicians, were assessed and compared on a pilot sample of 28 asthmatic children presented to the ED with acute asthma. The ICC coefficient was 0.85 (95% CI 0.76, to 0.94). This indicated a very good inter-rater reliability.

Evaluation of treatment effects

Hospital admission

In the overall study population, 75/458 (16.4%) of patients who received budesonide were admitted vs. 82/448 (18.3%) of those who received placebo, OR 0.84 (CI

0.58,1.23; p-value=0.38). Subgroup analysis did not also indicate any statistical significance, except for baseline severity with a score of ≥ 13 (will be referenced as severe group) vs. <13 (will be referenced as moderate group). Among the severe group 27/76 (35.5%) of patients who received budesonide were admitted vs. 39/73 (53.4%) of those who received placebo, OR 0.42 (CI 0.19,0.94; p-value=0.03). This implied a 58% reduction in the risk of admission in the budesonide vs. placebo group. Conversely, this also entailed a 2.4-fold increase in the likelihood of admission in the placebo vs. the budesonide group. Only 16.3% of patients who were randomized more than once had severe acute asthma. Their distribution was not different between the two study arms.

Asthma score change

There was a sustained drop of the asthma score during patients' stay in the ED in both groups, where maximum drop occurred during the first 2 hours. Overall, the mean drop in asthma score from baseline to disposition was not significantly different between the budesonide and the placebo groups, with mean difference of -0.19 in favor of the budesonide group (95% CI -0.42 to 0.04, p-value = 0.11). However, for the severe asthma group this drop was significantly lower in the budesonide vs. placebo treated subjects at disposition, with a mean difference of -0.73 (95% CI -1.33 to -0.13, p-value = 0.02) (Figure 2a). In addition; overall, the difference in the drop of asthma score between the two groups at 2, 3, or 4 hours was not significant (Figure 2b). However, in patients with severe asthma a steadily increasing difference in the drop of asthma score between the two study groups was noted starting from the second hour till the fourth hour when it reached -0.87 in favor of the budesonide group (95% CI -1.69 to -0.06, p-value = 0.04) (Figure 2c).

ED stay time

The mean stay time in the ED ($\pm$ SD) was 2.79 ± 0.85 hours for the budesonide group and 2.76 ± 0.84 hours for the placebo group. For patients with severe asthma the mean stay time in the ED ($\pm$ SD) was 3.36 ± 0.76 hours for the budesonide group and 3.38 ± 0.79 hours for the placebo group, and for patients with moderate asthma it was 2.67 ± 0.76 hours for the budesonide group and 2.64 ± 0.79 hours for the placebo group. None of these periods were significantly different between the two groups.

Adverse effects

The most frequently reported adverse effects were fine tremors (17 cases) and palpitations (11 cases). None of the reported adverse effects was serious and none was significantly different between the two groups.

Post-discharge follow-up

Among 744 discharged cases we were able to reach 641 (86.2%) by phone 72 hours post discharge. In 606 (94.5%) cases, improvement was reported, while 35 (5.5%) needed unscheduled visit to a health care facility. Among those, 8 patients were admitted to the hospital (3 in the budesonide group and 5 in the placebo group) and 27 were treated in the emergency department then discharged (16 in the budesonide group and 11 in the placebo group). There was no statistically significant difference between the two groups in their outcome at 72 hours post-discharge.

DISCUSSION

The largest and most recent trial among the very limited number of randomized and blinded studies that have previously examined the addition of ICS to systemic steroids in the treatment of acute asthma in the ED was by Upham et al (16). They studied 180 children with moderate to severe acute asthma and gave budesonide 2 mg in two divided doses. Using the same asthma score that we used, they found no difference in the admission rate, asthma score, and ED stay between the two study arms, which is consistent with our findings in the overall study population. However, when we examined patients with severe acute asthma, we found a significantly lower admission rate and asthma score in the budesonide group. In more practical terms, up to 7 patients would need to be treated with budesonide to save one admission as compared to placebo. This would highly be cost effective, since one-day admission of a patient with severe acute asthma in our institution costs around \$500 per night, while 3 doses of budesonide (500 mcg/dose) will only cost about \$7. This observation needs further studying. The advantage of ICS in patients with severe as compared to moderate acute asthma has been suggested in previous studies (21-23). Additionally, giving ICS to patients with acute asthma carries an educational message to continuing ICS during these episodes. The adverse effects reported in our study are likely to be due to the β -agonist (11).

A significant beneficial effect of high dose ICS in this setting is counterintuitive, since potent systemic corticosteroids were used in all patients (24). However, ICS were shown to act earlier than systemic corticosteroids. For example, a significant decrement in sputum eosinophils was reported in asthmatics after 2 hours from the administration of inhaled fluticasone as compared to oral prednisone (25). Moreover, a

reduction in airway responsiveness to adenosine 5'-monophosphate was demonstrated within 2 hours after a single inhalation of fluticasone (26). Such effects were presumed to be due to the topical non-genomic vasoconstrictor action of ICS (27, 28). Based on the clinical efficacy and pharmacokinetics of ICS, it would be reasonable to speculate that using an equivalent dose of a different ICS administered by pressurized metered-dose inhaler would have a similar effect (29-31).

In another interesting observation, we noticed that the relationship between the rate of admission and the patients' score was not linear. In other words, if we consider the asthma severity score range from 8 to 15 we find that, on average, one point drop in the score decreases the likelihood of admission by 2.6 folds, while looking only at scores ≥ 13 , one point drop will decrease it by 4.1 folds. This has to be kept in mind when interpreting changes in the asthma score.

There are several limitations to our study. Our positive results in relation to children with severe acute asthma need to be interpreted with caution because they were based on subgroup analysis, even though common confounders were taken into account when performing statistical analysis. Also, the definition of severe asthma was 12 according to the original score design, but our significant results were only demonstrated in patients with a score ≥ 13 . The point of distinction of severe from moderate exacerbation in the asthma score is arbitrary, nevertheless. We realize, however, that this was not a predefined point, giving another reason for cautious interpretation. Moreover, the re-enrolment of some subjects that was undertaken to increase the number of cases within our study time limitation could have introduced selection bias. Although this issue was taken into consideration during the statistical analysis by utilizing GLIMMIX technique, and the randomization balance was maintained. In

addition, we attempted to measure the peak expiratory flow rate in children >7 years old, but unfortunately only very few reliably performed the test. This was not so surprising (32) especially that most of our patients were not pre-trained to do it. Another limiting factor is that this is a single center study, which may limit the generalizability of results.

In conclusion, our study did not show beneficial effect of the use of high dose ICS as add-on therapy to the current regimen in the treatment of moderate to severe acute asthma in the first hour in the ED, but suggests a possible benefit in severe acute asthma.

ACKNOWLEDGEMENTS

Guarantor: Abdullah Alangari has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis including any adverse effects.

Author contributions: **Abdullah Alangari:** conception and design of the study, interpretation of data, and writing most of the manuscript. **Nidal Malhis:** study design, supervision and acquisition of data. **Mohamed Mubasher:** data analysis and writing the statistical section. **Najwa Al-Ghamdi:** study design and drug dispensing. **Mohamad Al-Tannir:** study design and data management. **Muhammad Riaz:** data analysis. **Dale T. Umetsu:** study design and manuscript preparation. **Saleh Al-Tamimi:** study design and supervision of data collection.

Financial disclosures: All the authors declare no conflict of interest.

Role of sponsor: The sponsor had no role in the design of the study, data collection, or data analysis.

REFERENCES

1. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006;**355**(21):2226-2235.
2. Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. *CMAJ* 2009;**181**(9):E181-190.
3. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000;**16**(5):802-807.
4. Tsai CL, Lee WY, Hanania NA, Camargo CA, Jr. Age-related differences in clinical outcomes for acute asthma in the United States, 2006-2008. *J Allergy Clin Immunol* 2012;**129**:1252-1258.
5. Pollack CV, Jr., Pollack ES, Baren JM, Smith SR, Woodruff PG, Clark S, et al. A prospective multicenter study of patient factors associated with hospital admission from the emergency department among children with acute asthma. *Arch Pediatr Adolesc Med* 2002;**156**(9):934-940.
6. GINA. Global Strategy for Asthma Management and Prevention; 2011.
7. EPR3. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma 2007 Aug.
8. Camargo CA, Jr., Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists in the treatment of acute asthma. *Cochrane Database Syst Rev* 2003(4):CD001115.
9. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. *Thorax* 2005;**60**(9):740-746.

10. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database Syst Rev* 2001(1):CD002178.
11. Edmonds ML, Milan SJ, Camargo CA, Jr., Pollack CV, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. *Cochrane Database Syst Rev* 2012;**12**:CD002308.
12. Rodrigo G. Rapid Effects of Inhaled Corticosteroids in Acute Asthma: An Evidence-Based Evaluation. *Chest* 2006;**130**(5):1301-1311.
13. Guttman A, Afilalo M, Colacone A, Kreisman H, Dankoff J. The effects of combined intravenous and inhaled steroids (beclomethasone dipropionate) for the emergency treatment of acute asthma. The Asthma ED Study Group. *Acad Emerg Med* 1997;**4**(2):100-106.
14. Sung L, Osmond MH, Klassen TP. Randomized, controlled trial of inhaled budesonide as an adjunct to oral prednisone in acute asthma. *Acad Emerg Med* 1998;**5**(3):209-213.
15. Nuhoglu Y, Atas E, Nuhoglu C, Iscan M, Ozcay S. Acute effect of nebulized budesonide in asthmatic children. *J Investig Allergol Clin Immunol* 2005;**15**(3):197-200.
16. Upham BD, Mollen CJ, Scarfone RJ, Seiden J, Chew A, Zorc JJ. Nebulized budesonide added to standard pediatric emergency department treatment of acute asthma: a randomized, double-blind trial. *Acad Emerg Med* 2011;**18**(7):665-673.
17. Sano F, Cortez GK, Sole D, Naspitz CK. Inhaled budesonide for the treatment of acute wheezing and dyspnea in children up to 24 months old receiving intravenous hydrocortisone. *J Allergy Clin Immunol* 2000;**105**(4):699-703.

18. Qureshi F, Pestian J, Davis P, Zaritsky A. Effect of nebulized ipratropium on the hospitalization rates of children with asthma. *N Engl J Med* 1998;**339**(15):1030-1035.
19. Hsu JC. Multiple Comparisons: Theory and methods First ed. Boca Raton, FL: Chapman & Hall/CRC; 1996.
20. Schall R. Estimation in generalized linear models with random effects. *Biometrika* 1991;**78**(4):719-727.
21. Schuh S, Dick PT, Stephens D, Hartley M, Khaikin S, Rodrigues L, et al. High-dose inhaled fluticasone does not replace oral prednisolone in children with mild to moderate acute asthma. *Pediatrics* 2006;**118**(2):644-650.
22. Schuh S, Reisman J, Alshehri M, Dupuis A, Corey M, Arseneault R, et al. A comparison of inhaled fluticasone and oral prednisone for children with severe acute asthma. *N Engl J Med* 2000;**343**(10):689-694.
23. Rodrigo GJ, Rodrigo C. Triple inhaled drug protocol for the treatment of acute severe asthma. *Chest* 2003;**123**(6):1908-1915.
24. Manser R, Reid D, Abramson M. Corticosteroids for acute severe asthma in hospitalised patients. *Cochrane Database Syst Rev* 2001(1):CD001740.
25. Belda J, Margarit G, Martinez C, Bellido-Casado J, Casan P, Torrejon M, et al. Anti-inflammatory effects of high-dose inhaled fluticasone versus oral prednisone in asthma exacerbations. *Eur Respir J* 2007;**30**(6):1143-1149.
26. Ketchell RI, Jensen MW, Lumley P, Wright AM, Allenby MI, O'connor BJ. Rapid effect of inhaled fluticasone propionate on airway responsiveness to adenosine 5'-monophosphate in mild asthma. *J Allergy Clin Immunol* 2002;**110**(4):603-606.
27. Horvath G, Wanner A. Inhaled corticosteroids: effects on the airway vasculature in bronchial asthma. *Eur Respir J* 2006;**27**(1):172-187.

28. Alangari AA. Genomic and non-genomic actions of glucocorticoids in asthma. *Ann Thorac Med* 2010;**5**(3):133-139.
29. Bisgaard H, Nikander K, Munch E. Comparative study of budesonide as a nebulized suspension vs pressurized metered-dose inhaler in adult asthmatics. *Respir Med* 1998;**92**(1):44-49.
30. Kelly HW. Establishing a therapeutic index for the inhaled corticosteroids: part I. Pharmacokinetic/pharmacodynamic comparison of the inhaled corticosteroids. *J Allergy Clin Immunol* 1998;**102**(4 Pt 2):S36-51.
31. Sims MW. Aerosol therapy for obstructive lung diseases: device selection and practice management issues. *Chest* 2011;**140**(3):781-788.
32. Ducharme FM, Davis GM. Measurement of respiratory resistance in the emergency department: feasibility in young children with acute asthma. *Chest* 1997;**111**(6):1519-1525.

Table 1. Asthma severity score (Qureshi et al).

Variable	Asthma score		
	1 point	2 points	3 points
Respiratory rate (breaths/min)			
2-3 years	≤ 34	35 - 39	≥ 40
4-5 years	≤ 30	31 - 35	≥ 36
6-12 years	≤ 26	27 - 30	≥ 31
>12 years	≤ 23	24 - 27	≥ 28
Oxygen saturation (%)	> 95 with room air	90 - 95 with room air	<90 with room air or supplemental oxygen
Auscultation	Normal breathing or end-expiratory wheezing	Expiratory wheezing	Inspiratory and expiratory wheezing, diminished breath sounds, or both
Retractions	None or intercostal	Intercostal and substernal	Intercostal, substernal, and supraclavicular
Dyspnea	Speaks in sentences or coos and babbles	Speaks in partial sentences or utters short cries	Speaks in single words or short phrases or grunts

Table 2. Comparison of baseline demographics and clinical characteristics of budesonide vs. placebo groups.

Baseline Characteristics	Budesonide (458)	Placebo (448)	P-value
	N (%)	N (%)	
Age (Years)			
2-6	305 (66.59)	310 (69.20)	0.40
7-12	153 (33.41)	138 (30.80)	
Gender (Females)	156 (34.06)	161 (35.94)	0.55
Family History of Asthma			
Parental (mother, father, or both)	208 (45.41)	199 (44.42)	0.76
Siblings (one or more)	328 (71.62)	301 (67.15)	0.15
Smokers at Home	83 (18.12)	86 (19.20)	0.68
Trigger (URI)	385 (84.06)	394 (87.95)	0.09
Children with Past Medical History of			
Admission to Ward or PICU (life time)	196 (42.79)	208 (46.43)	0.45
ED visits (last year)	243 (53.06)	219 (48.88)	
None	19 (4.15)	21 (4.69)	
Number of β2-agonist inhalations (or equivalent nebs) during the 6 hours prior to presentation			
5 or More	32 (6.99)	22 (4.91)	0.34
3-4	98 (21.40)	87 (19.42)	
1-2	161 (35.15)	155 (34.60)	
None	167 (36.46)	184 (41.07)	
Inhaled corticosteroids Prophylaxis	120 (26.20)	117 (26.12)	0.98
Montelukast Prophylaxis	31 (6.77)	33 (7.37)	0.73

Figure 1. Study Enrolment Chart. Eighty subjects were excluded because they declined to participate from the beginning and 110 declined after reading the consent form, which was fully explained.

Figure 2. a. Mean (with 95% CI) drop in asthma score from baseline in budesonide versus placebo groups at disposition time in all patients and by baseline asthma severity status. (*) Indicates significant p-value of 0.02 for patients with severe acute asthma. b. Mean (with 95% CI) drop in asthma score from baseline in budesonide versus placebo groups (taking all patients together) at the end of each hour time point of stay time in ED. c. Mean (with 95% CI) drop in asthma score from baseline in budesonide versus placebo subgroups at the end of each hour time point of stay time in ED according to baseline asthma severity. (*) Indicates significant p-value of 0.04 for patients with severe acute asthma at 4 hours time point.

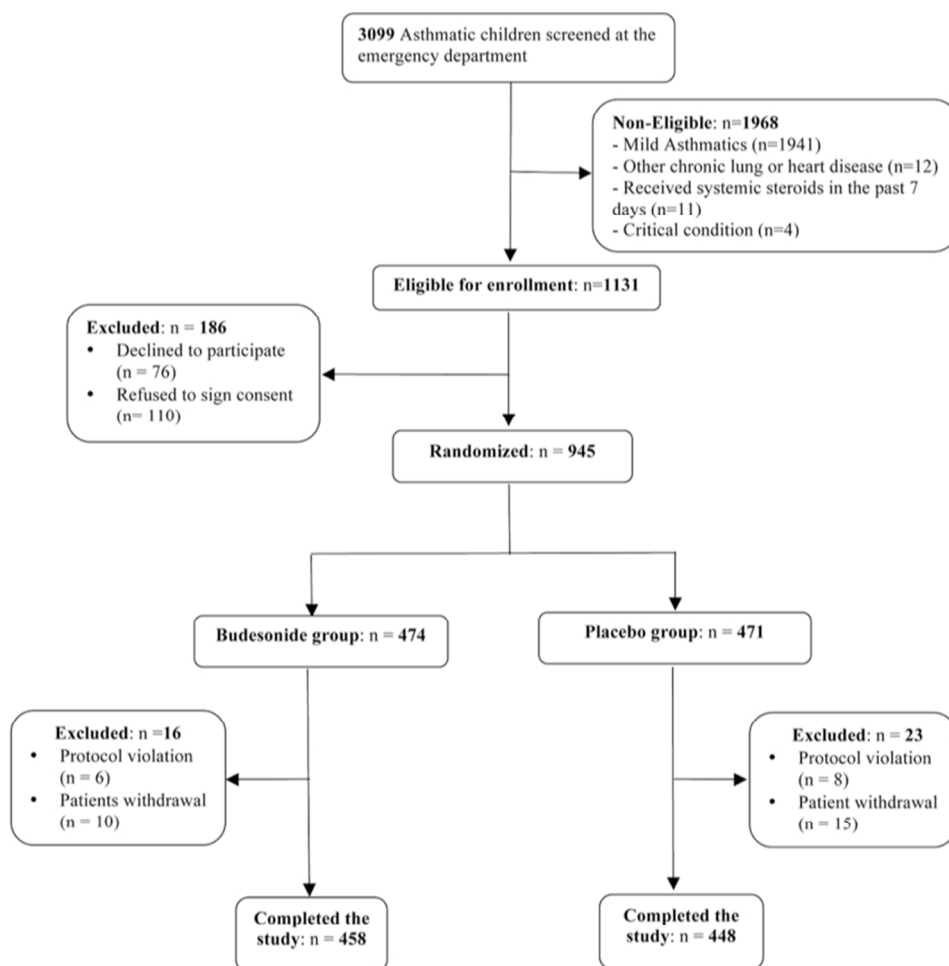


Figure 1. Study Enrolment Chart. Eighty subjects were excluded because they declined to participate from the beginning and 110 declined after reading the consent form, which was fully explained.
150x167mm (150 x 150 DPI)

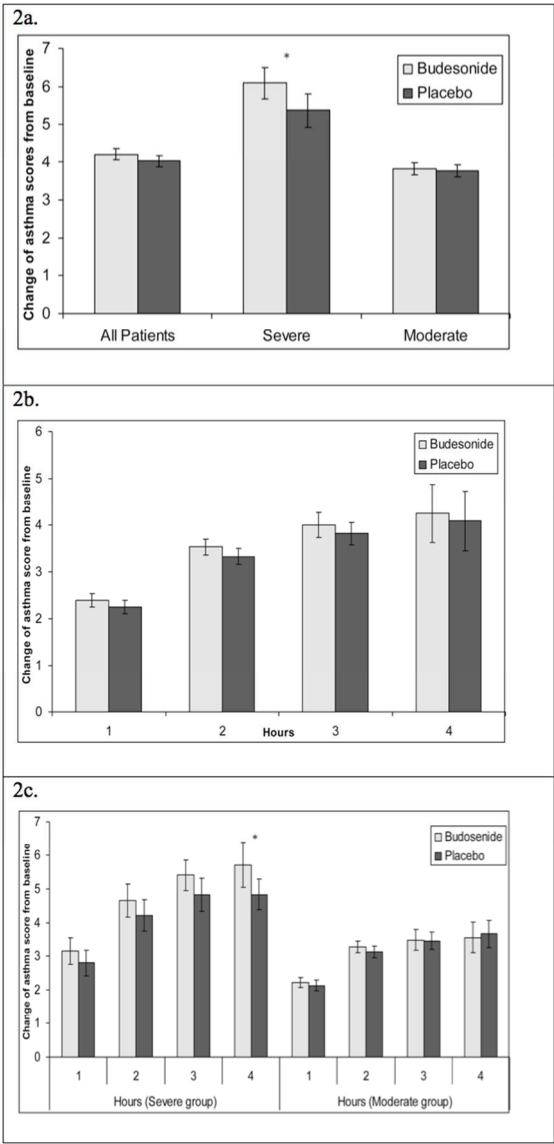


Figure 2. a. Mean (with 95% CI) drop in asthma score from baseline in budesonide versus placebo groups at disposition time in all patients and by baseline asthma severity status. (*) Indicates significant p-value of 0.02 for patients with severe acute asthma. b. Mean (with 95% CI) drop in asthma score from baseline in budesonide versus placebo groups (taking all patients together) at the end of each hour time point of stay time in ED. c. Mean (with 95% CI) drop in asthma score from baseline in budesonide versus placebo subgroups at the end of each hour time point of stay time in ED according to baseline asthma severity. (*) Indicates significant p-value of 0.04 for patients with severe acute asthma at 4 hours time point.

123x238mm (150 x 150 DPI)