Adding nebulized to systemic corticosteroids for acute asthma in children: a meta-analysis

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Abstract

International guidelines have recommended the use of inhaled beta-2 agonists and systemic corticosteroids (SC) as the first-line treatment for acute asthma. Objective: To evaluate the evidence for the efficacy of inhaled corticosteroids (ICS) in addition to SC compared to SC alone in children with acute asthma in the ED or during hospitalization. Data sources: Five electronic databases were searched. Study Selection: All RCTs that compared ICS (via nebulizer or metered dose inhaler) plus SC (oral or parenteral) with placebo (or standard care) plus SC were included without language restriction. Data extraction: Two reviewers independently reviewed all studies. The primary outcomes were hospital admission or hospital length of stay [LOS], and secondary outcomes were readmissions during follow-up, ED-LOS, lung function, asthma clinical score, oxygen saturation, and heart and respiratory rates. Results: Nine studies (n=1473) met the inclusion criteria. In all the studies, the ICS was budesonide. Compared to SC alone, adding budesonide to SC did not affect hospitalization rate, but decreased hospital LOS by more than one day (MD= -29.08 hours [-39.9 to -18.3]; I2=0%, p=<0.00001). Moreover, adding budesonide (especially with [?]2mg doses) significantly improved the acute asthma severity score among patients at ED. Conclusions: Compared to SC alone, adding budesonide to SC did not affect hospitalization rate, but decreases the LOS and improves the acute asthma score in children at ED setting.

INTRODUCTION

Childhood asthma is the most common chronic disease in childhood and a significant public health problem in the U.S. as well as in many other countries[1]. Despite relatively recent advances in our understanding of the inflammatory nature of the disease and the availability of highly effective medications to control their symptoms, many pediatric patients continue to experience poor asthma control with recurrent disease exacerbations[2].

Acute asthma has a significant impact not only on the utilization of health care and the quality of life of children and their families but also on a large percentage of disease costs[3]. Recent international evidence-based asthma clinical practice guidelines recommend the use of inhaled beta-2 agonists (SABA) and systemic corticosteroids (SC) as the first-line agents for acute asthma[4,5]. The efficacy of SC in acute asthma is well established, with a positive impact on several clinically meaningful outcomes, such as hospital admission rate, symptom scores, and the number of relapses after discharge from the emergency department (ED)[6]. However, the fact that despite SC use many children still require admission to hospital and that SCs have a slow onset of action (3–4 h after their administration) is a cause of concern among ED teams[7].

For this reason, the use of other anti-inflammatory therapies such as inhaled corticosteroids (ICS) for the treatment of acute asthma has been explored[6]. Potential benefits of ICS in acute asthma therapy might

include a rapid onset of action and a significant efficacy in diminishing airway reactivity and edema because of their direct delivery to the airways[8]. This is mainly because ICS, but not SC, cause immediate local bronchial mucosal vasoconstriction and inhibition of edema formation mediated by non-genomic mechanisms[9]. The main non-genomic mechanisms involve the activation of endothelial nitric oxide (NO) synthase and NO synthesis, which produce an increase in noradrenergic neurotransmission in the airway vasculature, with a consequent reduction in airway blood flow[10]. The decrease in airway blood flow is a desirable effect in asthmatic patients, given that they have significantly increased blood flow in the airway mucosa[11].

Therefore, the use of ICS for treating patients with acute asthma has become a subject of interest in recent years. There are reports showing the clear efficacy of ICS in the management of acute asthma when compared with a placebo[8,12]. In a recent systematic review with a meta-analysis that compared the efficacy of ICS with SC for acute asthma in children consulting in the ED or the equivalent, we found no significant differences between ICS and SC in terms of hospital admission rates, unscheduled visits for asthma symptoms, or need for an additional course of SC[12]. However, only a few studies have investigated the possibility of a beneficial effect of ICS added to SC, and the results have been conflicting, as was stated in a systematic review published in 2012, where only two RCTs carried out exclusively in a pediatric population were included[8].

Thus the present systematic review aims at updating and evaluating the available evidence for the efficacy of ICS (via nebulizer or metered dose inhaler [MDI]) in addition to SC compared to the standard therapy with SC for treating pediatric patients with acute asthma in the ED or during hospitalization.

METHODS

Search and selection criteria

This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO, http://www.crd.york.ac.uk/PROSPERO) as CRD42019133045. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to perform this review[13]. The authors identified studies published in MEDLINE, EMBASE, LILACS, CENTRAL and CINAHL databases, up to August 2019, using the terms "(((budesonide OR ciclesonide OR mometasone OR beclomethasone OR flunisolide OR fluticasone OR triamcinolone) AND (prednisone OR prednisolone OR hydrocortisone OR methylprednisolone OR dexamethasone OR betamethasone) AND (asthma exacerbations OR acute asthma OR acute wheezing OR wheezing exacerbations)))", filtered for children birth–18 yrs and clinical trials; language restrictions were not applied.

To be included, studies had to meet all of the following criteria: 1) children (preschoolers to adolescents) with asthma presenting with an acute asthma in the ED or hospitalized 2) randomized clinical trials (RCTs; parallel group or cross-over design) of any duration; 3) comparison of ICS (by nebulizer or MDI) *plus* SC (oral or parenteral) vs. placebo (or standard care)*plus* SC; and 4) a report of at least one of the following outcomes: primary outcomes: hospital admission (for ED studies) or hospital length of stay [LOS] (for hospitalized studies); and secondary outcomes: asthma clinical score, readmissions during the follow-up, ED-LOS, lung function, oxygen saturation (SpO_2), heart and respiratory rates, additional SABA requirements, and drug-related adverse effects [AEs] or severe adverse events [SAEs]. An SAE was defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization, or results in persistent or significant disability or incapacity[14].

We excluded studies that only involved patients experiencing their first wheezing episode or bronchiolitis and patients with other chronic respiratory conditions (e.g. bronchopulmonary dysplasia, cystic fibrosis, primary ciliary dyskinesia, and post-infectious bronchiolitis obliterans) or congenital cardiopulmonary conditions.

Data Extraction and Assessment of Risk of Bias

Titles, abstracts, and citations were independently analyzed by the authors (JC-R, CR-M). From the full text, all studies were independently assessed for inclusion. The authors were independently involved in all stages of study selection, data extraction, and risk of bias assessment. The latter was assessed according to recommendations outlined in the Cochrane Handbook[15] for the following items: 1) adequacy of sequence

generation; 2) allocation concealment; 3) blinding of participants and investigators; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective outcome reporting, and other bias. Disagreements were discussed and resolved by consensus.

Data Analysis

The analysis was performed on the basis of intention to treat and included all participants. Outcomes were pooled using mean differences (MD) (inverse variance method), standardized mean differences (SMD) for similar outcomes measured in different scales, and Mantel-Haenszel risk ratios (RR). When significant data was reported only in median and IQR, mean and SD were estimated according to the literature[16], and the estimation was pooled in the meta-analysis; all estimated data will be properly identified. Estimate precision was quantified by 95% confidence intervals (CI). Heterogeneity was measured by the I^2 test ([?]25% absence of bias; 26 to 39% unimportant; 40% to 60% moderate; and 60% to 100% substantial bias)[17]. A fixed-effects model was used when there was no evidence of significant heterogeneity in the analysis (I^2 <40%); if significant heterogeneity was found, a random-effects model was used[18,19]. *A priori* subgroup analyses included: setting (ED vs. hospitalized), age (preschooler vs. school-age), acute asthma severity score, doses of ICS, type of SC, and sponsored (pharmaceutical industry vs. independent). The meta-analysis was performed with Review Manager 5.3.5 software (Cochrane IMS, 2014).

RESULTS

A total of 41 studies were identified after duplicates were removed, and 32 studies were excluded based on the title and the abstract (11 were not performed for acute asthma, 13 did not use systemic corticosteroids in both groups, 5 did not specify the data for children, and 2 RCTs did not include intervention drugs). We performed a full text review of nine articles, [20-28] all of which met our inclusion criteria and were counted in the quantitative and qualitative analyses (Figure 1).

Included Studies

These nine studies[20-28] were published between 1998 and 2017. A summary of the characteristics of the included studies is shown in Table 1. Three were done in Turkey[22,26,28]and one in each of the following countries: Canada[20], US[23], Saudi Arabia[25], Venezuela[27], Brazil[21], and Bangladesh[24]. All of the studies were of parallel-group design, eight trials[20-26,28] were double-blinded, and one was a simple blinded trial[27]. Six studies were performed in the ED[20,22,23,25,27,28]and three in hospitalized children[21,24,26]. Two studies[20,27] were performed in the ED but also had some information for admitted patients, and one[27] of those studies had a three-intervention-group design, but we included only information for our comparison criteria (ICS + SC vs. SC). One study[25] allowed the inclusion of patients previously included in the study. All the studies included an asthma clinical severity score, but the score varied between studies (Table 1). Four studies[20,23,25,28] reported funding information, and all of them were independently sponsored (not by the pharmaceutical industry). All except two studies[21,22] had high methodological quality (Figure 2).

Participants

Selected studies included 1473 patients, who presented 1656 episodes of acute asthma. A higher percentage of males than females were enrolled in all the studies (Table 1). The age range of the enrolled patients was between 0.58 yrs. to 13 yrs. Two studies[21,26] reported younger patients (mean age 12.4 months[21] and 19 months[26]); however, none of them enrolled patients with bronchiolitis or first wheezing episode.

Four studies[20,25,26,27] reported the family history of asthma (12% to 75% of the patients included had a positive family history). Only two studies[26,28] reported the positive asthma predictive index (API) status (30–38% had positive API). Six studies[20,22,23,25,26,28] reported the use of ICS in the past (range from 20% to 100%). Sung et al.[20] and Upham et al.[23] stratified patients according to the use of ICS, while Nuhoglu et al.[22] and Alangari et al.[25] only reported the prevalence of ICS used. In the Razi et al.[26] trial, the use of ICS was a mandatory inclusion criterion, but in the Razi et al.[28] trial, patients with budesonide more than 400 mcg/day or those who change their doses in the last 2 months were excluded. The acute asthma severity

scores at randomization were moderate to severe in four studies[23-26], but using different clinical scores (Table 1).

Intervention

In seven studies[20,22,23-26,28], a comparison was made between ICS+SC and SABA vs. saline solution (as a placebo)+SC and SABA. Only two studies[21,27] included different interventions for comparison: Kassisse et al.[27] included no placebo and Sano et al.[21] compared ICS+SC and SABA vs. ipratropium bromide+SC and SABA. All the studies performed in the ED used nebulized budesonide as the ICS in the intervention group at various total doses from 1 mg to 3 mg (administrated in two or three nebulizations). Two[21,26] out of three of the hospitalized studies described the use of nebulized budesonide during hospitalization (2mg/day up to 5 days in Razi et al.[26]and "0.25 mg of inhaled budesonide suspension 4 times daily to a total dose of 1 mg/d throughout the hospitalization period" in Sano et al.[21]). All the studies included SC as the standard care for both intervention and control groups (Table 1).

Primary Outcomes

a. Hospital admission in ED studies: Five studies[20,23,25,27,28] reported information for this outcome. In the pooled data of the four studies[20,23,25,27] that reported absolute admission data, there was a tendency to favor budesonide for reducing the risk of hospital admission, but it did not reach a significant difference (RR= 0.89 [95% CI: 0.74 to 1.07], I^2=0%, p=0.21) (Figure 3). This result was similar using random effect model (RR=0.92 [0.77-1.09), p=0.34). Razi et al.[28] reported a significantly higher discharge rate in the budesonide than in the placebo group (survival analyses: log-rank=12.407, p<0.001).

In the subanalysis of studies that included only moderate to severe acute asthma episodes[23,25], there was no significant difference in hospital admission between the budesonide and placebo groups (RR= 0.88 [0.68 to 1.14], I^2=47%, p= 0.34). In the subanalysis of ICS doses (budesonide [?] 2 mg vs. < 2mg), there was no significant difference in hospital admission between groups (RR=0.89 [0.71 to 1.11], I^2=26%, p=0.29 vs. RR=0.89 [0.67 to 1.19], p=0.44).

b. Hospital LOS: Four studies[20,21,26,27]reported data for this outcome. Pooled data from two studies[21,26] that reported hospital LOS in hours showed a significant reduction in LOS for those who received budesonide rather than controls (MD = -29.08 hours [-39.9 to -18.3]; I^2=0%, p=<0.00001) (Figure 4). This result was similar using random effect model (data not shown). The other study[20]reported a survival analysis where children who received budesonide were released from the ED or discharged from the hospital significantly more rapidly than were those who received placebo (log rank test, p = 0.02); but Kassisse et al.[27] reported no significant difference.

Secondary Outcomes

a. Acute asthma severity score in ED and hospitalized studies: Although all the studies included information for this outcome, they were analyzed separately according to the setting, type of score, and how it was reported. The two big trials[23,25] done in the ED included difference in score, without giving the basal or post-intervention score, precluding the possibility to include their data in the overall score meta-analysis of ED studies. There was no significant difference in the asthma score between the budesonide and the control group in these two trials (Figure 5a). This result was similar using random effect model (RR=-0.13 [-0.38 to 0.12), p=0.30). The other four studies done in ED[20,22,27,28] reported post-intervention data; when the data was reported in median and IQR, we estimated mean and SD according to the literature[16]. We found that children from the budesonide group significantly improved their asthma score compared with the placebo group in the ED studies[20,22,27,28] (SMD: -0.30 [-0.53 to -0.06], p=0.01, I^2=27%), Figure 5b. This result was similar using random effect model (SMD: -0.31 [-0.60 to -0.02), p=0.04). In the subanalysis comparing doses of budesonide ([?]2mg vs. <2 mg), the pool data of ED studies showed a significant improvement in acute asthma severity score in the budesonide vs. placebo group, but clearly this effect was driven by the studies using [?]2 mg (Figure 5c).

Among studies performed in trials with hospitalized children, one study[24] showed a significant differences

in the asthma score at 1 hour, 2 hours and 3 hours from intervention favor to budesonide vs placebo group (7.36±1.03 vs 9.18±1.01 p<0.01 at 1h, 5.91±0.52 vs 7.30±1.05 p<0.01 at 2 h, 5.42±0.50 6.36±0.70 p<0.01 at 3 h, respectively). The other trials[21,26] only gave graphics but not data on asthma score. One study[21] reported a significantly reduction in the clinical score for the budesonide, but the other[26] did not.

b. LOS in ED studies: Three studies[20,25,28] reported data for this outcome. There was not significantly difference in LOS between the budesonide and control groups MD= -0.26 [-0.88 to 0.35]; I^2= 91%, p=0.40).

c. Readmissions during follow-up: Four studies[20,21,23,25] included data for this outcome. There was no significant difference in readmission during the follow-up (overall OR=0.89 [0.36 to 2.25]; I2 = 0%, p=0.81).

d. Lung function: Only two studies[22,24]reported this outcome and both measured the peak expiratory flow rate (PEFR). Nuhoglu et al.[22] reported an increased mean of PEFR in the budesonide vs. placebo group (72.50 ± 23.8 vs. 47.86 ± 18.9, p=0.02). Similarly, Akhtaruzzaman et al.[24] reported significantly more improvement in the % of predicted PEFR value in the budesonide vs. placebo group at 1,2 and 3 hour after treatment (76.63 ± 1.4 vs. 69.30 ± 1.1, p=<0.01; 77.42 ± 1.2 vs. 71.42 ± 1.1, p=<0.01; and 78.58 ± 1.1 vs. 72.36 ± 1.0, p=<0.01, respectively).

e. SpO_2: Four studies done in ED[20, 23,27,28] reported data for this outcome. The pooled data of two studies[23,27] showed no difference in the mean change from baseline among budesonide vs. control group (data not shown). Similarly, Sung et al.[20] reported no difference. However, Razi et al.[28] showed significant higher SpO_2 at 120 min post-intervention in the budesonide vs. placebo group (95% [93–98] vs. 91.5% [90–96], p=0.012).

Among studies performed in trials with hospitalized children, Akhtaruzzaman et al.[24] found a significant difference at 1, 2, and 3 hrs. after intervention favorable for the budesonide vs. placebo group (95.15% ± 0.71 vs. 94.12% ± 0.89, p <0.01; 95.55% ± 0.71vs. 94.45% ± 0.83, p<0.01; and 95.94% ± 0.35 vs. 94.76% ± 0.66, p<0.01, respectively).

f. Heart and respiratory rates: Three studies[20,23,28] done at ED and one in hospitalized children[24]reported data for heart rate. The pooled data of two ED studies[23,28] showed no significant difference in overall heart rate change between the budesonide and control groups (MD = -1.08 [-6.48 to 4.32]; I^2 = 0%, p=0.70). Also, Sung et al.[20] reported that there were no differences between groups. The study performed in hospitalized children[24] showed a significant lower heart rate at 1, 2, and 3 hrs. after intervention favorable to budesonide vs. placebo group (102.18±6.58 vs. 109.09±5.48, p <0.01; 88.42±5.36 vs. 96.85±5.24, p<0.01; 83.64±3.86 vs. 93.52±4.56, p<0.01, respectively).

Four studies[21,23,24,27] reported data for the respiratory rate. There was no significant change in pooled data for respiratory rate among studies done in ED[23,27] (MD = 0.43 [-1.43 to 2.29]; I^2 = 0%, p=0.65). However, among trials with hospitalized children, Sano et al.[21]reported significantly higher respiratory rates at 24, 36, and 48 hrs. among children in the control group (who received ipratropium bromide) than those in the budesonide group; and Akhtaruzzaman et al.[24] reported a significant lower respiratory rate at 1, 2, and 3 hrs. after intervention favorable to budesonide vs. placebo group (24.97±3.25 vs. 27.82±4.10, p <0.01; 23.55±2.77 vs. 25.27±3.35,p <0.01; and 22.42±1.79 vs. 24.48±2.74, p <0.01, respectively).

g. Additional SABA requirement: Only one study[20] reported this outcome, showing no difference in additional salbutamol use between groups.

h. Adverse events: Six studies[20,23-27]reported AE data, and four studies[20,24,26,27] reported no occurrence of AEs. Upham et al.[23] reported a total of 106 AEs in 62 patients (33 in the budesonide and 29 in the control group). Alangari et al.[25] described 28 AE episodes, 17 cases of fine tremors (7 in the budesonide and 10 in the control group), and 11 cases of palpitations (6 in the budesonide and 5 in the control group); these details were described in their protocol document (NCT01524198).

DISCUSSION

To our knowledge, this is the first meta-analysis of trials exclusively carried out in

children and adolescent populations that explored the efficacy of adding ICS to SC compared with SC alone for acute asthma when consulting in the ED or during hospitalization. Our study demonstrates that in children hospitalized with an acute asthma episode adding budesonide significantly reduces the LOS by more than one day. Among the trials done in the ED, adding budesonide significantly improved the acute asthma severity score, especially when using high doses of budesonide ([?]2 mg).

Objective measurements such as SpO_2 and respiratory and heart rates were significantly different between children treated with the addition of budesonide versus controls. The SpO_2improved, while respiratory and heart rates decreased in the budesonide group only among trials with hospitalized children; however, not pooled data analysis was able to performed. It is important to mention that heart rate could be influenced by the SABA drugs included in the protocol. In terms of lung function, only two studies (one in the ED and one in hospitalized children) reported this outcome, and in both children on ICS+SC significantly improved the PEFR in comparison with SC. The same result was before described in adults using PEFR, but not with FEV1[8]. Similarly, the present review shows that adding budesonide to SC does not result in more AEs or SAEs, as was described in the last Cochrane review[8].

The most recent GINA guidelines[4] stated that a high dose of ICS within the first hours after presentation to ED reduces the need for hospitalization in patients who did not receive SC, but the addition of ICS to SC is inconclusive, and the type of ICS, doses, and duration remain unclear; moreover, the cost is an issue that remains to be resolved. Likewise, the latest Cochrane review[8] of five studies (n=433 patients), but only two studies[20,23] in children, showed that ICS plus SC significantly reduces hospital admission compared with SC, but with high heterogenicity (OR=0.54 [0.36 to 0.81], I^2=52%), and stated the necessity for further research "to clarify the most appropriate drug dosage and delivery device, and to define which patients are most likely to benefit from ICS therapy". Our systematic review of nine studies done exclusively in a population of children with acute asthma (n=1473) showed that adding budesonide via nebulizer did not reduce hospital admission, but significantly reduces the LOS, and improves the asthma severity score in the ED, especially when using high doses of budesonide. In terms of cost, in a recent cost-effectiveness analysis done in a middle-high income country, we demonstrated that ICS in addition to SCs compared with standard therapy with SCs for treating pediatric asthma model showed that compared to SCs, therapy with ICS+SCs was associated with lower total costs (US$ 88.8 vs.US$97.7 average cost per patient) and a lower probability of hospital admission (0.9060 vs. 0.9000)[29].

The biological explanation of the superiority of adding ICS to SC vs. SC is the addition of the non-genomic effect, which only ICS exhibit (i.e. activation of endothelial NO synthase and NO synthesis, increasing the noradrenergic neurotransmission in the airway vasculature and therefore reducing the airway blood flow[10], a desirable effect in asthmatic patients, where a significant increased blood flow in the airway mucosa ocurrs[11]), to the genomic effect of SC. Another advantage of adding ICS is their very rapid onset of action (in minutes) in contrast to the slow onset of action of SCs (3–4 h after administration). An additional mechanism is that ICS administration simultaneously with SABA could acutely potentiate its bronchodilation effect[30].

In all the RCTs included in this systematic review, the ICS used was budesonide. A study in vivo[31] showed that budesonide oleate is formed rapidly in human airways after inhalation and is detectable in lung tissue for almost 2 days after a single inhalation. Esterification takes place intracellularly within the lungs, and the sustained action of budesonide is explained by this fatty acid conjugation. This sustained retention of esterified budesonide in the lungs supports the prolonged duration of action of budesonide and its suitability for once-daily administration[31]. Budesonide, compared with other ICS, had the highest vasoconstrictive effect in airway blood flow[32,33], and since airway blood flow is increased in asthmatics, the vasoconstrictive effect of ICS is beneficial. Also, when budesonide was nebulized up to 26% of the drug is systemically bioavailable in children[34].

This study has several limitations. First, no studies using ICS delivery by MDI were found, and therefore the results of budesonide via nebulizer cannot be extrapolated to ICS delivery via MDI or to other types of ICS. Also, it was not possible to evaluate the relative efficacy of the different nebulizer devices used in these trials. Second, only two studies measured lung function. Third, differences in type of SC was not analysis in

detail. Fourth, the minimal clinically important difference for each asthma score using in the trials was not reported. Five, since better results were obtained using 2mg doses of budesonide, more trials with higher doses need to be performed. The strength of this study is that it includes nine RCTs exclusively carried out in a population of children, most of them with high-quality methodology, from seven different countries around the world involving more than 1400 patients with asthma.

In conclusion, adding budesonide to SC, compared with SC alone, for acute asthma in hospitalized children significantly reduces the LOS by more than one day, and significantly improves the acute asthma severity score for patients in the ED (especially using [?]2 mg).

List of Abbreviations: AEs= adverse effects, API= asthma predictive index, ED= emergency department, ICS= inhaled corticosteroids, LOS= length of stay, MDI= metered dose inhaler, NO= nitric oxide, PEFR= peak expiratory flow rate, RCTs= randomized clinical trials, RR= risk ratios, SAEs= severe adverse effects, SABA= beta-2 agonists, SpO_2= oxygen saturation, SC= systemic corticosteroids, SMD= standardized mean differences.

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FIGURE LEGENDS:

Figure 1. Process of study selection.

Figure 2. Risk of bias of the eligible studies.

Figure 3. Pooled RRs and 95% CIs for overall hospital admissions in ED studies.

Figure 4. Pooled MDs and 95% CIs for LOS in hospital studies

Figure 5.a. Pooled MDs and 95% CI in the difference for acute asthma severity score in ED studies (mean differences).

Figure 5.b. Pooled SMD and SMD95% CI for acute asthma severity score in ED studies (mean after intervention).

Figure 5.c. Pooled SMD and SMD95% CI for acute asthma severity score in ED studies according by budesonide doses.

Figure 1. Process of study selection.

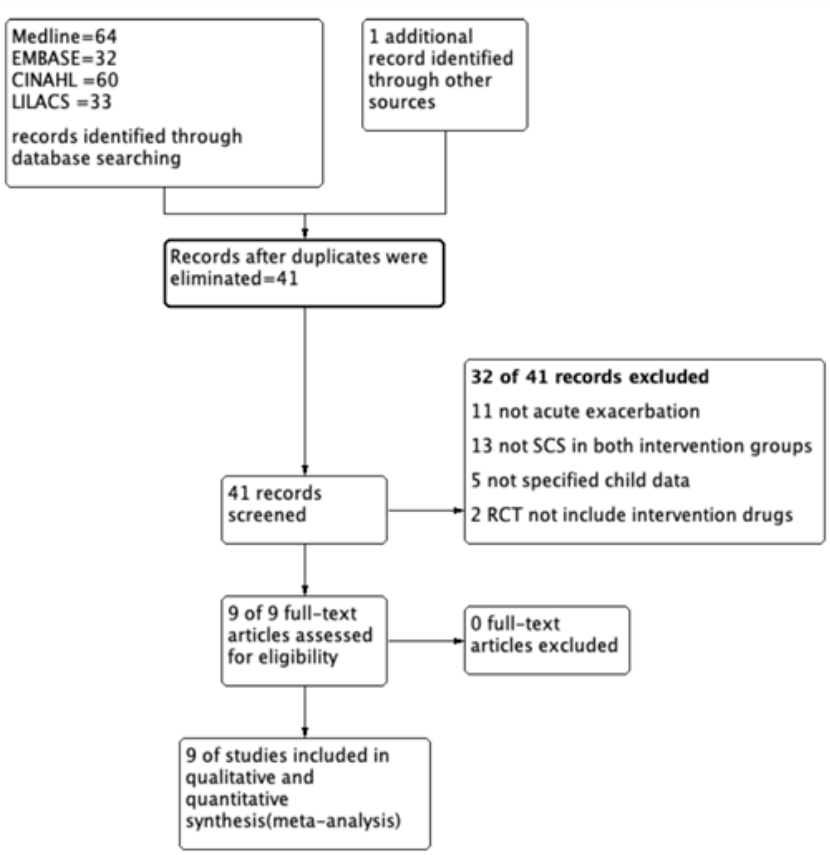

Figure 2. Risk of Bias of the Eligible Studies.

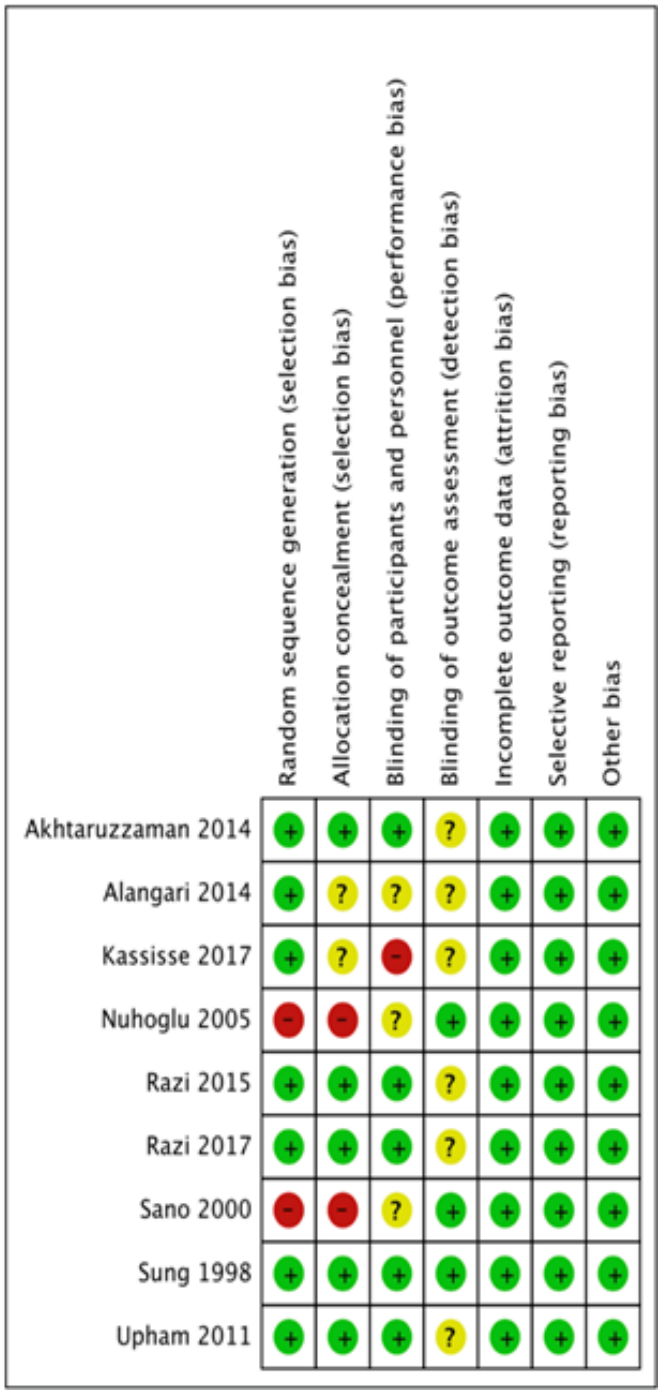

Figure 3. Pooled RRs and 95% CIs for overall hospital admissions in ED studies.

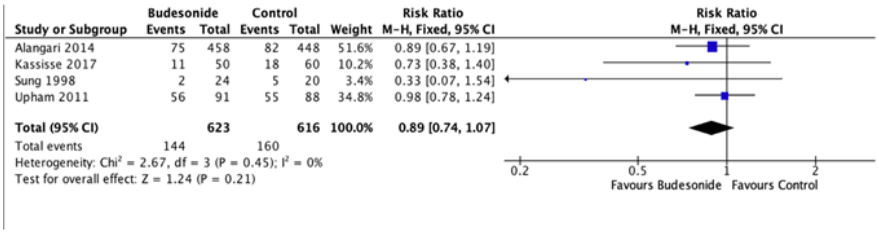

Figure 4. Pooled MDs and 95% CIs for LOS in hospital studies.

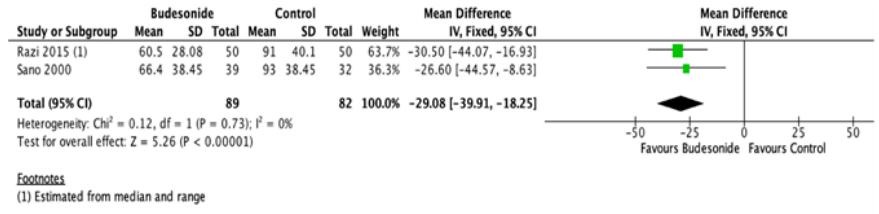

Figure 5.a. Pooled MDs and 95% CI in the difference for acute asthma severity score in ED studies (mean differences).

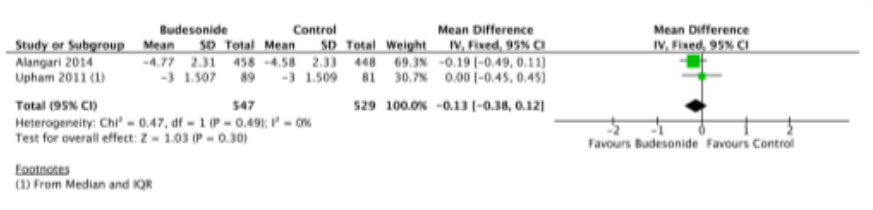

Figure 5.b. Pooled SMD and SMD95% CI for acute asthma severity score in ED studies (mean after intervention).

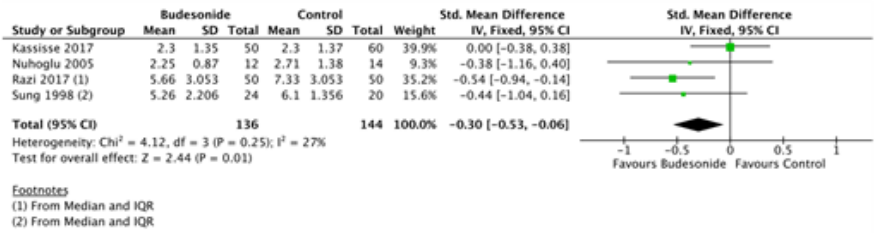

Figure 5.c. Pooled SMD and SMD95% CI for acute asthma severity score in ED studies according by budesonide doses.