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ORIGINAL ARTICLE

Principal findings of systematic reviews of acute asthma treatment in childhood

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Abstract

Objective: The objective of this study is to summarize the principal findings in the literature about acute asthma management in children. **Methods:** Systematic reviews of randomized clinical trials (SRCTs) with or without meta-analysis in children (1–18 years) admitted to the emergency department (ED) were retrieved using five data bases. Methodological quality was determined using the AMSTAR tool. **Results:** One hundred and three studies were retrieved. Among those, 28 SRCTs were included: seven SRCTs related to short-acting beta2-agonists (SABA), three to ipratropium bromide (IB), eight to corticosteroids, one to racemic adrenaline, one to leukotriene receptor antagonists (LTRA), four to magnesium sulfate, one to intravenous (IV) SABA, one to IV aminophylline, one to IV ketamine, and one to antibiotics. It was determined that administering SABA by MDI-VHC is superior to using a nebulizer, because it decreases the hospital admission rate, improves the clinical score, results in a shorter time in the ED, and causes fewer adverse effects. Levalbuterol and albuterol were similar. In patients with moderate to severe exacerbations, IB+SABA was superior to SABA, decreasing hospital admission and improving the clinical score. SABA heliox administered by nebulizer decreased exacerbation severity compared to oxygen. Inhaled corticosteroids (ICS), especially administered by nebulizer, showed results similar to oral corticosteroids (OCS) with respect to reducing hospital admission, unscheduled visits, and the requirement of additional systemic corticosteroids. ICS or OCS following ED discharge was similar with regard to relapse. Compared with a placebo, IV magnesium reduced hospital admission and improved lung function. **Conclusions:** SRCTs are useful for guiding decisions in acute asthma treatment.

Keywords

Acute asthma management, adolescent, AMSTAR, asthma exacerbation, children, meta-analysis, systematic review, treatment

History

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Introduction

Systematic reviews of randomized clinical trials (SRCTs) are scientific investigations with pre-planned methods and a collection of original studies as their “subjects.” They synthesize the results of multiple primary investigations using strategies to identify bias and random error [1]. Evidence-based practice guidelines are based on SRCTs appropriately adapted to local health circumstances. Therefore, well-conducted SRCTs can be useful in guiding clinicians in choosing the most effective treatment for acute asthma in children [2].

However, more than 100 SRCTs for asthma management in children have been published, making reading all of them a

time-consuming process. Therefore, putting together all this evidence could be useful for most clinical practitioners in the field. The objective of this article is to summarize the principal findings of the SRCTs for acute asthma in children. We followed the step order for acute asthma management set out by the principal international guidelines [2–4].

Methods

We identified the published studies in MEDLINE, EMBASE, CINAHL, SCOPUS, and the Cochrane Controlled Trials Register (up to October 2014) database, using the terms: ((asthma) AND (acute exacerbation) AND (Meta-Analysis or Systematic Review) AND (Child or Children)). Studies published solely in abstract form were excluded because the methods and results could not be fully analyzed.

To be included, studies had to meet all the following criteria: (a) systematic review of randomized clinical trials (SRCTs) (with or without meta-analysis) without language

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restriction (only the latest version was considered); (b) inclusion of children (1–18 years) or in a mixed population (adults and children) with recurrent wheezing or asthma who visited the ED or equivalent due to an acute asthma exacerbation; and (c) studies of pharmacological treatment of acute asthma. Reviews of safety/security or prevention management, chronic asthma treatment, cost/efficacy studies, or non-pharmacological treatment were excluded.

Data extraction and assessment of risk of bias

Titles, abstracts, and citations were independently analyzed by two authors (J. C. R. and C. R. M.). Based on the full text form, all the studies were evaluated for inclusion criteria, type of intervention, population included, study design, and outcomes. After obtaining full reports about potentially relevant trials, eligibility was assessed. The pooled estimate of the principal and secondary outcomes with their 95% confidence interval (CI), I^2 statistic, and number need to treat (NNT) are presented only if they were available for pediatric patients. The methodological quality of the systematic reviews was assessed using the AMSTAR (Assess Systematic Reviews) tool [5]. The AMSTAR tool has a maximum of 11 points, 8, or more points being considered a good quality SRCT. Disagreements were discussed and resolved by consensus.

Results

One hundred and three studies were retrieved from the databases. Among those, 28 were included. 21 were related to the first line of treatment: seven to short-acting beta2-agonists (SABA), three to ipratropium bromide (IB), eight to corticosteroids, one to adrenaline, and one to leukotriene receptor antagonists (LTRA). Seven were related to the second line of treatment: four to magnesium sulfate (three to intravenous [IV] and one to nebulize), one to IV salbutamol, one to IV

aminophylline, one to ketamine, and one to antibiotics (Figure 1). Their methodology using the AMSTAR tool is shown in Table 1.

First line of treatment

SABA

SABA delivery by metered-dose inhaler (MDI) with spacers versus nebulizers. Castro-Rodriguez and Rodrigo [6] compared the efficacy of SABA administered by MDI with a valved holding chamber (VHC) or nebulizer in children under 5 years of age with moderate to severe exacerbations of wheezing or asthma presenting at the ED (RCTs = 6, $n = 491$). SABA by MDI+VHC significantly decreased the admission rate (primary outcome) compared with SABA by nebulizer (OR = 0.42; 95% CI [0.24–0.72], $p = 0.002$, $I^2 = 0\%$; NNT = 10, 95% CI [6–26]). This decrease was even more significant among children with moderate to severe exacerbations (OR = 0.27; 95% CI [0.13–0.54]; $p = 0.0003$). Also, the clinical score significantly improved in the group who received SABA by MDI+VHC compared with a nebulizer (SMD = -0.44 ; 95% CI [-0.68 to -0.20], $p = 0.0003$, $I^2 = 24\%$).

Later, Cates et al. [7] compared adults and children >2 years of age who were randomized for SABA by MDI with a spacer or SABA by nebulizer (RCTs = 15 in children, $n = 1879$). In children, the hospital admission rate (primary outcome) did not differ between groups. However, those on SABA by MDI with spacer spent significantly less time in the ED (MD = -33.5 min, 95%CI [-43.3 to -23.7], $p < 0.00001$, $I^2 = 66\%$) and had fewer AEs (MD = -5.41 , 95%CI [-8.34 to -2.48], $p = 0.0003$, $I^2 = 53\%$ for rise in the pulse rate; and RR = 0.64, 95%CI [0.44–0.95], $I^2 = 0\%$ in tremor) compared with a nebulizer. No differences between groups were found for peak expiratory flow (PEF) and forced volume in the first second (FEV₁) at 30 min. and at the end of the study. No difference in oxygen saturation was found (six RCTs); however, in one RCT, children who used a nebulizer suffered more desaturation compared with MDI and spacer (25% versus 9%, $p = 0.006$).

Albuterol versus levalbuterol. Jat and Khairwa [8] evaluated the efficacy and safety of albuterol versus levalbuterol in all age groups. Seven RCTs totaling 1625 participants were selected (6/7 RCTs included children between 1 and 18 years of age, $n = 998$). Respiratory rate, oxygen saturation, percentage of change in FEV₁, clinical asthma score, and AEs were not different between groups.

SABA versus formoterol as relief medication. Rodrigo et al. [9] evaluated the efficacy and safety of inhaled formoterol compared with SABAs (three out of nine RCTs included 165 children 5–15 years old; two RCTs compared formoterol versus salbutamol, and one formoterol versus terbutaline). Children received 1–3 doses of 12–24 mcg of formoterol. No difference could be detected in pulmonary function at the end of the treatment (primary outcome) between formoterol and SABAs, with no difference between adults and children in the sensitivity analysis. Likewise, there were no differences

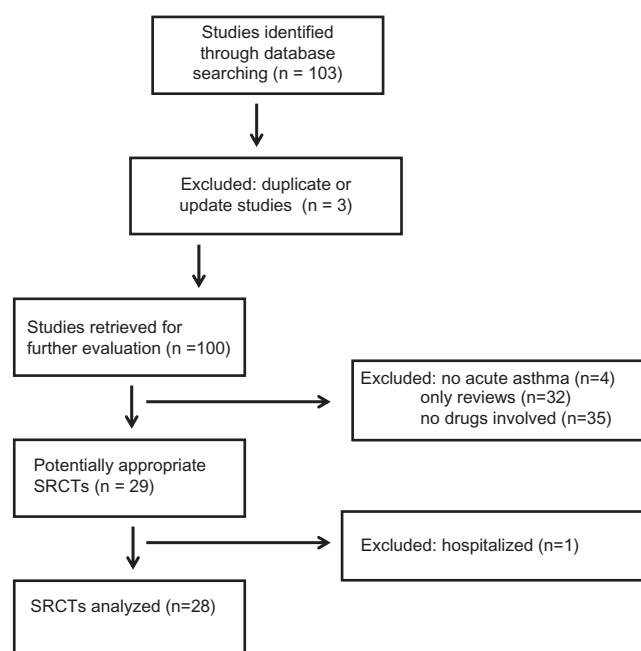


Figure 1. Flowchart for identification of usable systematic reviews of randomized clinical trials (SRCTs).

between treatments for serum potassium levels, heart rate, QT interval corrected for heart rate, hospitalization rate, or total withdrawals; however, no pooled data exclusively for children was available for these secondary outcomes.

Simultaneously, Welsh and Cates [10] assessed the efficacy and the safety of formoterol as relief therapy compared with SABA (eight RCTs, $n = 22\,604$ children and adults). However, there was insufficient pediatric data presented to merit a full subgroup analysis.

SABA by nebulizer driven by oxygen versus heliox. Rodrigo et al. [11] studied the effect of adding heliox to standard medical care (one of seven RCTs were done in children). In this study ($n = 18$ children aged 16 months–17 years), patients received either an 80:20% helium–oxygen gas mixture or room air (control) at 10 L/min by nonrebreathing face mask. Inhaled heliox significantly lowered pulse paradoxus ($23.3 \pm 6.8 - 10.6 \pm 2.8$ mmHg, $p < 0.001$), increased PEF rate ($69.4\% \pm 12.8\%$, $p < 0.05$), and lowered the dyspnea index ($5.7 \pm 1.3 - 1.9 \pm 1.7$, $p < 0.001$). Moreover, inhaled heliox spared intubation in three patients. No apparent AEs were described.

Recently, Rodrigo and Castro-Rodriguez [12] evaluated the efficacy of heliox versus oxygen in driving SABA nebulization in patients with acute severe asthma (three out of 10 RCTs were done in 113 children aged 2–18 years old). The mean duration of heliox therapy was 120 min, and the

most common helium–oxygen mixture used was 70:30%. The analysis of pooled pediatric studies showed that β_2 -agonist heliox-driven nebulization significantly decreased the severity of exacerbations (SMD = -0.74 , 95% CI $[-1.45$ to $-0.03]$, $p = 0.04$, $I^2 = 69\%$). No differences for serious AEs between groups were found.

IB

IB versus placebo. Teoh et al. [13] studied the effectiveness of inhaled IB alone versus control in six RCTs ($n = 411$ children 2–18 years old). Inhaled IB was delivered using nebulizers in four studies and MDI+VHC in two studies. Children who received IB alone experienced significantly higher failure compared with SABA (OR = 2.27, 95% CI $[1.08 - 4.75]$, $p = 0.03$, $I^2 = 0\%$). Likewise, treatment failure was higher in those using IB alone compared with IB combined with SABA (OR = 2.65, 95% CI $[1.2 - 5.88]$, $p = 0.016$, $I^2 = 16\%$). The use of IB was not associated with significant AEs.

IB versus SABA. Rodrigo and Castro-Rodriguez [14] evaluated the effectiveness of a combination of IB and SABA compared with SABA alone (16 of 32 RCTs were done in children 5 months–17 years old, $n = 1564$). Data from children showed significant reductions in hospital admissions (RR = 0.73; 95% CI $[0.63 - 0.85]$, $p = 0.0001$, $I^2 = 0\%$;

Table 1. Evaluation the quality of the 28 systematic reviews includes in the study using AMSTAR tool [5].

Ref./AMSTAR's questions	1	2	3	4	5	6	7	8	9	10	11
Castro-Rodriguez et al. [6]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
Cates et al. [7]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Jat et al. [8]	Y	Y	Y	Y	N	Y	Y	Y	Y	NA	Y
Rodrigo et al. [9]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Welsh et al. [10]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Rodrigo et al. [11]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N
Rodrigo et al. [12]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Teoh et al. [13]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Rodrigo et al. [14]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Griffiths et al. [15]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Rodrigo et al. [16]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N
Su et al. [17]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Edmonds et al. [18]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Beckhaus et al. [19]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
Quon et al. [20]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Edmonds et al. [21]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
Rowe et al. [22]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Edmonds et al. [23]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Edmonds et al. [24]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Watts et al. [25]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Powell et al. [26]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Rowe et al. [27]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N
Mohammed et al. [28]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Shan et al. [29]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Travers et al. [30]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Travers et al. [31]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Jat et al. [32]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Graham et al. [33]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y

AMSTAR, Asses Systematic Reviews; Ref., reference; Y, yes; N, no; CA, cannot answer; NA, not applicable.

AMSTAR's Questions: (1) Was an "a priori" design provided? (2) Was there duplicate study selection and data extraction? (3) Was a comprehensive literature search performed? (4) Was the status of publication (i.e., grey literature) used as an inclusion criterion? (5) Was a list of studies (included and excluded) provided? (6) Were the characteristics of the included studies provided? (7) Was the scientific quality of the included studies assessed and documented? (8) Was the scientific quality of the included studies used appropriately in formulating conclusions? (9) Were the methods used to combine the findings of studies appropriate? (10) Was the likelihood of publication bias assessed? (11) Was the conflict of interest included?

NTT = 13, 95% CI [9–28]), increase in spirometric parameters 60–120 min after the last treatment (SMD = -0.54 ; 95% CI $[-0.28$ to $-0.81]$, $p = 0.0001$, $I^2 = 57\%$), and reduction in clinical score (SMD = -0.29 ; 95% CI $[-0.51$ to $-0.07]$, $p = 0.01$, $I^2 = 0\%$). There was no increase of AEs in children treated with IB.

Later, Griffiths and Ducharme [15] studied whether the addition of inhaled IB to SABAs provided clinical improvement and reduced AEs in children (20 RCTs, $n = 2697$ children 18 months–18 years old). Most trials used a fixed-dose protocol of three doses of 250 mcg or two doses of 500 mcg of nebulized IB in combination with SABA over 30–90 min, while three trials used a single dose and two used a flexible-dose protocol, according to the need for SABA. Children experienced a lower risk of admission to hospital if they were treated with the combination of inhaled SABAs plus IB versus SABA alone (RR = 0.73, 95% CI [0.63–0.85], $p < 0.0001$, $I^2 = 0\%$; NNTB = 16, 95% CI [12–29]). Patients treated with this combination also showed significant improvement in % predicted FEV₁ at 60 min (MD = 10.08, 95% CI [6.24–13.92], $p < 0.0001$, $I^2 = 0\%$) and at 120 min (MD = 6.87, 95% CI [1.17–12.56], $p = 0.018$, $I^2 = 0\%$), in clinical score at 120 min (SMD = -0.23 ; 95% CI $[-0.42$ to $-0.04]$, $p = 0.018$, $I^2 = 0\%$), and less risk of nausea and tremor than for SABA alone.

Adrenaline

Adrenaline versus SABA. Rodrigo and Nannini [16] evaluated the efficacy of aerosolized adrenaline compared with SABA (one of six RCTs were done in children 1–17 years of age, $n = 120$). In this pediatric study, patients were randomly allocated to receive either salbutamol or racemic epinephrine by nebulization at 0, 20, and 40 min. All patients received oral steroids (OCS). There was no difference between groups for the pulmonary index score, length of stay, hospital admissions, or relapse rate. However, the adrenaline group exhibited significantly fewer nasal side effects than the SABA group.

Corticosteroids

Systemic (SC) versus inhaled corticosteroids (ICS). Su et al. [17] compared ICS versus placebo or OCS in children (10 RCTs, $n = 829$ children 4–11 years of age). Four studies compared ICS with a placebo, four studies compared ICS with SC, and two studies compared ICS plus SC with SC. The rate of hospital admissions (primary outcome) in children treated with ICS was not significantly higher than those with OCS. The rate of hospital admissions in children with ICS was significantly lower than those on a placebo (OR = 0.15, 95% CI [0.03–0.93], $p = 0.042$, $I^2 = 0\%$).

Edmonds et al. [18] studied the benefit of ICS given in the ED for adults and children. Thirteen of 32 RCTs done on children without severe asthma were selected for the primary analysis (ICS versus placebo, with no SC given to either group, or ICS versus placebo, with SC given to both groups). Children (seven RCTs, $n = 583$) treated with ICS were less likely to be admitted to hospital from the ED (primary outcome) (OR = 0.52; 95% CI [0.33–0.80]; $p = 0.0033$, $I^2 = 59\%$). Subgroup analysis of hospital admissions (children

and adults) based on concomitant SC use revealed that both subgroups showed a benefit from ICS in reducing hospital admissions (five RCTs with 433 participants, ICS + SC versus SC: OR = 0.54; 95% CI [0.36–0.81], $p = 0.003$, $I^2 = 52\%$; and seven RCTs with 527 participants, ICS versus placebo: OR = 0.27; 95% CI [0.14–0.52], $p < 0.00001$, $I^2 = 0\%$). There was a significant benefit for ICS versus placebo at 3–4 h for improving FEV₁ and during the first 4 h for improving PEF_R, but no sub-analysis for pediatric population was performed. There were no significant AEs for ICS. In the secondary analysis (ICS alone versus SC alone), eight out of 14 RCTs were done on children ($n = 569$), but heterogeneity among the studies complicated data pooling and drawing conclusions.

Recently, Beckhaus et al. [19] compared the effects of ICS with those of SC in children aged 2–18 years. Eight RCTs ($n = 797$) were included. All used prednisolone as SC and budesonide, fluticasone, dexamethasone, and flunisolide as ICS. No significant difference between ICS and SC was found in terms of primary outcomes: hospital admission, unscheduled visits for asthma symptoms, and the need for an additional SC course. However, analyzing a single study with nebulized ICS, those children treated with budesonide had significantly less need for an additional course of SC than those on SC (RR: 0.12, 95% CI [0.02–0.91], $p = 0.04$). On the contrary, when compared with the other three RCTs, which used ICS by MDI versus SC, children on ICS by MDI had a significantly higher need for an additional course of SC than those on SC (RR: 3.35; 95% CI [1.2–9.4], $p = 0.02$, $I^2 = 0\%$). The change in % of predicted FEV₁ at the 4th hour was significantly higher for the SC group (WMD: 7.75; 95% CI [2.93–12.57], $p = 0.002$, $I^2 = 0\%$), but no difference between groups was detected after this time. There was insufficient data on the length of ED stay during the first visit and scores. Vomiting was similar between groups.

Increased versus stable doses of ICSs. Quon et al. [20] compared the effectiveness of increasing the dose of ICS versus keeping the usual maintenance dose as part of a patient-initiated action plan at the onset of asthma exacerbations (five RCTs in children and adults, $n = 1250$ children 6–14 years old). There were no overall differences in the need for rescue OCS or in the overall risk of AEs when patients were randomized for increased ICS compared with stable maintenance dose groups. However, no pooled data were available for these outcomes based exclusively on children.

Corticosteroids following discharge from ED. Edmonds et al. [21] examined the effect of using ICS instead of OCS for patients discharged from the ED after treatment for acute asthma (four of seven RCTs were done on children 6 months–16 years old, $n = 542$). All studies compared high-dose fluticasone or budesonide versus oral prednisolone or prednisone. There were no overall differences between the treatments with respect to relapse rate. However, since only one of the four pediatric studies reported this outcome, no pooled data were available. Likewise, there were no overall differences in secondary outcomes such as the use of SABA, quality of life, or AEs. However, the sample size was not adequate to prove equivalence between treatments, and severe patients were excluded.

Later, Rowe et al. [22] studied the benefit of corticosteroids (OCS, intramuscular [IM], or IV) in patients discharged from an acute care setting (i.e., usually the ED). Six RCTs ($n=374$ adults and children, only two RCTs were done exclusively in children, $n=71$) were included. One study used IM corticosteroids and five studies used OCSs (3–10 d). However, no specific analysis comparing the pediatric population was done. Significantly fewer patients in the corticosteroid group relapsed, needing additional care in the first week (RR = 0.38, 95% CI [0.2–0.74], $p=0.004$, $I^2=0\%$; NNT = 10, 95% CI [8–23], but there was no contribution of the pediatric population to this main outcome. This favorable effect was maintained over the first 21 d (RR = 0.47; 95% CI [0.25–0.89], $p=0.02$), and there were fewer subsequent hospitalizations (RR = 0.35, 95% CI [0.13–0.95], $p=0.04$, $I^2=0\%$). Patients receiving corticosteroids had less need for SABA (mean difference = -3.3 activations/d; 95% CI [-5.6 to -1.0], $p=0.045$, $I^2=0$). Changes in pulmonary function tests and side effects in the first 7–10 d, although rarely reported, showed no significant differences between groups. No difference between IM and oral corticosteroids was found.

Recently, Edmonds et al. [23] studied the effectiveness of ICS therapy on acute asthma following ED discharge, when used in addition to, or as a substitute for, standard OCS therapy (five of 12 RCTs were done on 549 children aged 1–16 years). When comparing ICS plus OCS versus OCS alone, no differences for relapses, quality of life, symptom scores, or AEs were found between the two groups. Likewise, there were no differences for ICS alone versus OCS with respect to relapse rates, admissions to hospital, or secondary outcomes for the use of SABA, symptoms, or adverse events. However, no pooled data exclusively for children was available for these outcomes.

Edmonds et al. [24] studied the benefit of ICS for asthma managed in the ED in 32 RCTs (21 RCTs were done on 1403 children aged 6 months–18 years: 13 RCTs comparing ICS versus placebo and eight RCTs comparing ICS versus systemic corticosteroids). The dose, frequency, and ICS varied widely; however, in all the cases, ICS were administered early in the course of ED treatment, usually at the time of the first SABA treatment, and the route of administration was via nebulizer or MDI with spacer. There was a significant reduction in hospital admissions (primary outcome) for children ($n=583$) treated with ICS when compared with those treated with a placebo (OR = 0.52, 95% CI [0.33–0.80], $p=0.003$, $I^2=59\%$). No pooled data were available for secondary outcomes (e.g. lung function or clinical score) based exclusively on pediatric patients.

Leukotriene receptor antagonists (LTRA)

Watts and Chavasse [25] studied whether the addition of LTRA (montelukast or zafirlukast) produces a beneficial effect in acute asthma (eight RCTs on children aged 2–12 years old) who are currently receiving SABA ($n=1470$) and SC ($n=470$). LTRA administration was IV in three RCTs and oral in five RCTs. No differences in hospital admission or in secondary outcomes between LTRAs (IV or oral) and the control group were found.

Secondary line of treatment

Magnesium sulfate

Nebulized magnesium sulfate. Powell et al. [26] studied the efficacy of inhaled magnesium sulfate administered in acute asthma on pulmonary function and admission rates (seven out of 16 RCTs, $n=159$ children, 2–16 years old). Children received one to three doses of (2–2.5 ml) isotonic magnesium sulfate solution (6.3%). There was no difference in the change of FEV₁ or hospital admission between inhaled magnesium sulfate and SABA compared with SABA alone.

IV-magnesium sulfate. Rowe et al. [27] examined the effect of IV magnesium sulfate in patients with acute asthma treated in the ED (two out of five RCTs were done on children 1–18 years old, $n=78$). Children received 25 mg/kg or 100 mg/kg (up to a maximum of 2 g) IV magnesium sulfate over 20 min. For children within the severe asthma subgroup, hospital admissions for those treated with magnesium sulfate were significantly lower compared with a placebo at the end of the study period (OR = 0.09; 95% CI [0.01–0.56]). Although there were significant overall improvements in secondary outcomes such as PEF_r and FEV₁ in patients with acute severe asthma, no pooled data were available for these outcomes based exclusively on pediatric patients. No clinically important changes in vital signs or AEs were reported.

IV versus nebulized magnesium sulfate. Mohammed and Goodacre [28] estimated the effect of IV and nebulized magnesium sulfate on hospital admissions and pulmonary function (seven of 24 RCTs were done on 284 children 1–18 years of age; five RCTs by IV and two RCTs by nebulization). Children received 25–100 mg/kg (with a maximum of 2.5 g) magnesium sulfate IV over 20–35 min or 2.0–2.5 ml isotonic magnesium sulfate (6.3%) solution by nebulization. IV magnesium sulfate in children with moderate to severe asthma exacerbations was associated with a significant effect on respiratory function (SMD = 1.94, 95% CI [0.80–3.08]; $p=0.001$, $I^2=84\%$) and a significant decrease in hospital admission (RR = 0.70, 95% CI [0.54–0.90]; $p=0.005$, $I^2=7.3\%$). On the contrary, nebulized magnesium sulfate was not associated with an effect on lung function or hospital admissions.

Recently, Shan et al. [29] estimated the effects of IV and nebulized magnesium sulfate on adults and children with acute asthma (six of 25 RCTs included 244 children aged 1–18 years old; five RCTs using IV and one RCT using nebulizer). Children received 25–100 mg/kg (maximum 2.5 g) magnesium sulfate IV over 20–35 min or 2.5 ml isotonic magnesium sulfate (6.3%) solution in a single dose with SABA by nebulization. In children with moderate to severe asthma exacerbations, IV magnesium sulfate was associated with significant effects on respiratory function (SMD = 1.94, 95% CI 0.80–3.08, $p=0.0008$) and hospital admissions (RR = 0.70, 95% CI 0.54–0.91, $p=0.008$, $I^2=7\%$). The only pediatric study of nebulized magnesium sulfate performed on children (mild-to-moderate asthma exacerbations) showed no effect on respiratory function or hospital admission.

IV SABA

Travers et al. [30] studied the benefit of adding IV SABA to inhaled SABA therapy for acute asthma treated in the ED (two of three RCTs were done on 75 children aged 1–17 years old). Children received terbutaline IV (loading dose of 10 mg/kg/min over 10–20 min and then as a continuous infusion of 1 mg/kg) or salbutamol IV (15 mcg/kg over 10 min). While one pediatric RCT showed no difference between groups for outcomes such as improvement in clinical score, time spent on continuous nebulized salbutamol, and length of stay in the pediatric ICU, the other showed significant differences in recovery time, oxygen requirement, and time for discharge from the ED. However, no pooled data were available for these outcomes in children.

IV-aminophylline

Travers et al. [31] compared the benefit of IV SABA versus IV aminophylline for acute asthma treated in the ED and inpatients with acute severe asthma (five of 11 RCTs were done on 197 children aged 1–15 years old). The two pediatric RCTs that reported the length of stay (one in the pediatric ICU) did not show a difference between groups. Individual separate analysis for the two studies indicated no difference between aminophylline and SABA for this outcome. However, this finding should be interpreted with caution due to the small number of trials and the limited opportunities for aggregating the data of these studies.

IV-ketamine

Jat and Chawda [32] evaluated the efficacy of ketamine compared with a placebo (one RCT, 68 non-intubated children up to 18 years presenting in the ED) in children with severe acute asthma who had not responded to standard therapy. No difference in respiratory rate, oxygen saturation, hospital admission rate, or need for mechanical ventilation between the ketamine group (0.2 mg/kg IV bolus over 1–2 min, followed by a 0.5 mg/kg/h continuous infusion for 2 h) and the placebo group was found. Also, there was no difference in AEs or need for other adjuvant therapy or in the Pulmonary Index Score between the groups.

Antibiotics

Graham et al. [33] determined the efficacy of antibiotics for exacerbations of asthma in adults and children (one of the two RCTs was done on children, *n* = 44). Children received either hetacillin or a placebo. The clinical course and improvement of airway function were similar between groups. Only 20% of patients had a viral or mycoplasma infection.

Discussion

As a consequence of an extensive review of 28 SRCTs on acute asthma treatment and considering only those results based on pediatric data, we constructed a recommendation for the best treatment for acute asthma in children (Table 2). SABA administered by MDI-VHC is superior to SABA by nebulizer for decreasing hospital admission rate, improving the clinical score, shortening the time spent in the ED, and producing fewer side effects. Levalbuterol is similar to

Table 2. Principal findings of the 28 systematic reviews of randomized clinical trials included.

Outcomes	SABA	IB	RA	Corticosteroids	LTRA	MgSO ₄
Reduction hospital admission	By MDI-VHC > Neb	IB < SABA IB + SABA > IB IB + SABA > SABA	RA by Neb = SABA by Neb	ICS = OCS ICS > placebo ICS at discharge > placebo ICS = OCS at discharge	LTRA = placebo	MgSO ₄ by IV > placebo MgSO ₄ by Neb = placebo
Improvement of clinical scores Need for additional SC	By MDI-VHC > Neb	IB + SABA > SABA	RA by Neb = SAB by Neb	ICS = OCS ICS by Neb > OCS	LTRA = placebo LTRA = placebo	
Shorter time spent ED Improvement of lung function Side effects	By MDI-VHC > Neb By MDI-VHC > Neb By MDI-VHC < Neb	IB + SABA > SABA IB + SABA < SABA	RA by Neb = SAB by Neb RA by Neb > SAB by Neb		LTRA = placebo	MgSO ₄ by IV > placebo

> (better than); < (lower than); = (equal to); + (plus). ICS, inhaled corticosteroids; IV, intravenous; IB, ipratropium bromuro; MgSO₄, magnesium sulfate; MDI-VHC, metered doses inhaler-valvulated holding chamber; Neb, nebulization; OCS, oral corticosteroids; RA, racemic adrenaline; SABA, short-acting beta2-agonists; LTRA, leukotriene receptor antagonists.

albuterol. Children on IB have more failures compared to those on SABA, a result similar to the use of IB alone versus IB plus SABA. In patients with moderate to severe asthma exacerbations, IB plus SABA is superior to SABA alone in reducing hospital admissions, improving lung function, and improving the clinical score, and has a lower risk of nausea and tremor. Racemic epinephrine or SABA (both by nebulization) are similar for pulmonary index score, length of stay, and hospital admissions, with minor nasal side effects in the adrenaline group. SABA heliox-driven nebulization significantly decreased the severity of exacerbations compared to SABA oxygen-driven nebulization. Insufficient pediatric data for formoterol as a relief medication preclude any recommendation. Among corticosteroids, ICS and OCS are similar with respect to reducing hospital admission rate, unscheduled visits for asthma symptoms, and need for an additional course of SC, but when ICS is given by nebulization it produces a lower need for an additional course of SC compared with OCS. ICS is superior to a placebo with respect to decreasing the hospital admission rate. No data for an exclusive pediatric population are available for comparing increased versus stable doses of ICS for acute asthma exacerbations. ICS following discharge from the ED results in a significant reduction in hospital admission compared to a placebo; however, ICS was similar to OCS. Finally, LTRA (orally or IV) is not useful in reducing hospital admission or secondary outcomes.

Unfortunately, there is less evidence to guide second-stage treatment. Magnesium sulfate administered by nebulization is not useful; however, when administered by IV it results in fewer hospital admissions and better lung function compared with a placebo. No pooled data are available for IV SABA or for IV aminophylline compared with IV SABA. IV ketamine shows results similar to a placebo.

Even though all the 28 SRCTs included in the present review had a good methodological qualification (AMSTAR: $\geq 8/11$ points), it is important to take into consideration that these SRCTs were built from RCTs. As we know, asthma clinical research, or RCTs, lack adequate outcome standardization. As a result, care should be taken when comparing and interpreting various SRCTs. It is important to mention that the majority of the SRCTs (22/28) included were published relatively recently (less than 7 years ago).

For trials of acute management of asthma exacerbations in ED settings, the 2012 Asthma Workshop (sponsored by the NIH and the Agency for Healthcare Research and Quality) recommends the use of validated assessment tools such as the Pediatric Asthma Severity Score, the Pulmonary Score, the Preschool Respiratory Assessment Measure, the Clinical Asthma Score, the Pulmonary Index, and the Asthma Severity Score for children under 12 years of age, and the use of FEV₁ for children ≥ 12 years of age (and for children 5–11 years if feasible) [34]. However, those tools were not uniformly used in these 28 SRCTs.

Another consideration for SRCTs is the assessment of heterogeneity among the RCTs included in the analysis. For testing the homogeneity of the outcome and effect measurements between studies being meta-analyzed, most SRCTs used both the Chi² test for heterogeneity (Cochrane *Q* test) and the *I*² statistic ($p < 0.10$ in the former or $I^2 > 40\%$ was

deemed indicative of significant heterogeneity). If significant heterogeneity was present, a random-effects model was used to aggregate the outcome effect measurement; otherwise, a fixed-effect model was reported [35]. Most of the 28 SRCTs correctly reported the heterogeneity.

SRCTs on the safety/security of antiasthmatic drugs were not included in the present review, nor were SRCTs comparing different devices for drug administration (e.g. spacers or nebulizers). Management of acute asthma in children hospitalized on a ward or in the intensive care unit is beyond the scope of this report. A review of SRCTs on pharmacologic chronic treatment of asthma has previously been published [36].

The limitation of this review was the impossibility of identifying some particular characteristics that physicians would take into account when they choose a certain therapy for their patients, e.g. ethnicity, atopy status, asthma severity using the pre-established score systems mentioned, different modalities of oxygen therapy, and more details when compared with corticosteroids administration (e.g. early during first hour versus later, 3 versus 5 d after ED discharge). Other issues were the scarcity of pediatric data for second-line therapies (e.g. IV SABA, IV aminophylline or IV ketamine, and magnesium sulfate by nebulization in preschoolers) and the impossibility of pooling data for some primary outcomes.

Conclusion

This review of 28 SRCTs gives us the opportunity to highlight the best pharmacological treatment for acute asthma in children (Table 2), which is largely in accordance with those proposed by the main international guidelines, with the one exception that GINA [2] and the British [4] guidelines consider nebulized isotonic magnesium sulfate as additional options in the first hour of treatment for children older than 2 years with severe exacerbation.

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Declaration of interest

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