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ASTHMA EXACERBATION IN CHILDREN : A SYSTEMATIC REVIEW

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Abstract

According to the definition provided by the Global Initiative for Asthma (GINA), asthma is a chronic inflammatory illness of the airways. This disorder involves the participation of a large number of cells, most notably mast cells, eosinophils, and T lymphocytes. People who are susceptible to the condition have frequent episodes of wheezing, chest tightness, shortness of breath, and coughing, typically late at night or first thing in the morning. These symptoms are typically related to extensive but variable airway blockage, which is at least partially reversible both on its own and with treatment. This obstruction can occur either spontaneously or as a result of treatment. A hyperreactive response of the airways to a variety of stimuli has also been linked to the inflammation. Wheezing is one of the most common symptoms. It is characterized by a high-pitched, whistling musical sound that is produced by turbulence in the airflow. The wheezing heard on the patient's dying breath is the least severe type. Wheezing does not occur during the most severe episodes due to the restriction of airflow that is connected with the narrowing of the airways and the tiredness of the respiratory muscles. A beta2 agonist, azithromycin, inhaled corticosteroids, and antimuscarinic may be recommended to patients under the age of 18 who are experiencing acute exacerbations of their asthma.

Keyword: *Airflow retriction, Asthma, Children, Corticosteroids, Exacerbation*

INTRODUCTION

An episode of acute or subacute airflow restriction that occurs against the backdrop of chronic airway inflammation and airway hyperresponsiveness is what medical professionals refer to as an asthma exacerbation. An asthma trigger is what sets off an exacerbation, which worsens asthma symptoms such as wheezing, coughing, dyspnea, and respiratory distress.[1,2] The exacerbation is begun by a trigger that promotes bronchoconstriction and increased mucus production. There are a variety of variables that can put a child at risk for developing asthma, including genetic and prenatal risk factors, environmental triggers, and host characteristics.[3]

In the early years of a person's life, wheezing is extremely common; however, only a tiny percentage of infants and young children who wheeze will go on to develop asthma in their later years of childhood and adolescence.[2] The presence or absence of atopy, the temporal patterns of symptoms, the triggers of symptoms, the illness severity, the patterns of airway inflammation, and the response to treatment are some of the factors that have been used to explain the various early-childhood wheezing phenotypes. However, there is still a significant gap in our capacity to identify young children who are at high risk of having chronic asthma.[3–5]

Even though there have been significant advancements in the treatment of asthma, asthma exacerbations in children continue to be a significant problem. They have the potential to significantly increase the morbidity and death rates of patients. According to data collected in real life in the Netherlands on the incidence of severe asthma exacerbations in children receiving primary care, it was found that four out of every 1000 children with asthma would experience a severe exacerbation per follow-up year, and that 25% of children who have experienced one severe asthma exacerbation would experience another one within the following year.[5,6]

There are currently a large number of pharmacological interventions that can be used to treat asthma exacerbations; however, there is a significant variation in the management of asthma exacerbations that is expressed in guideline recommendations versus clinical practice.[7,8] This variation influences diagnostic and treatment decisions for both the clinician and the patient. In the pediatric population, we wanted to take a close look at the diagnostic and treatment approaches taken for asthma exacerbations and see how well they stacked up.

METHODS

Protocol

Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines were adhered to in a manner that ensured this investigation's methodology was carried out in a manner that was compatible with the suggestions stated by those standards.

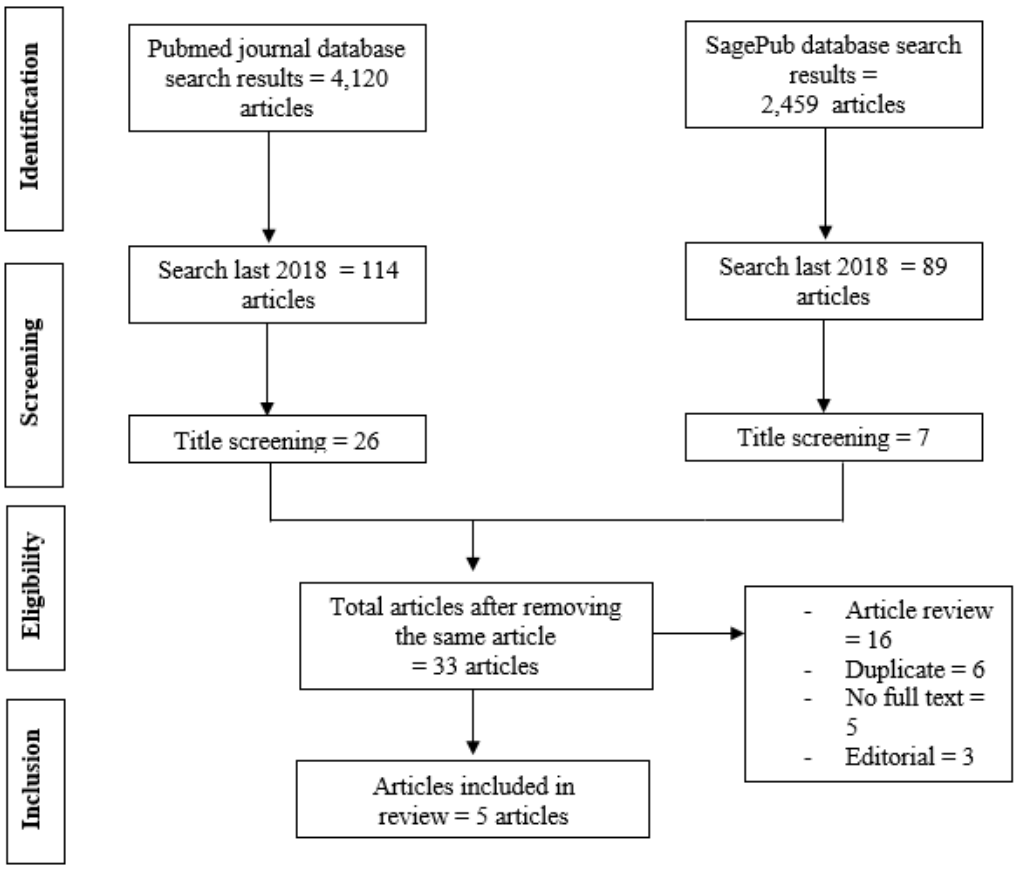

Figure 1. Article search flowchart

Criteria for Eligibility

This literature review seeks to investigate the asthma exacerbation in children by evaluating or analyzing prior studies on the issue. This is a significant problem raised by the present investigation. Researchers participate in studies that satisfy the following requirements: 1) To be accepted for publication, publications must be published in English and focus on the asthma exacerbation in children. 2) This assessment included articles published after 2015 but prior to the period covered by this systematic review. Examples include editorials, submissions without a DOI, already published review articles, and entries that are substantially similar to those previously published in a journal.

Search Strategy

The search for studies to be included in the systematic review was carried out from February, 1st 2023 using the PubMed and SagePub databases by inputting the words: “asthma exacerbation” and “children”. Where *("asthma"[MeSH Terms] OR "asthma"[All Fields] OR "asthmas"[All Fields] OR "asthma s"[All Fields]) AND ("exacerbate"[All Fields] OR "exacerbated"[All Fields] OR "exacerbates"[All Fields] OR "exacerbating"[All Fields] OR "exacerbation"[All Fields] OR "exacerbations"[All Fields] OR "exacerbator"[All Fields] OR "exacerbators"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields])* is used as search keywords.

Data retrieval

Following the completion of a literature review that involved the reading of the titles and abstracts of previously carried out research, the author modified the criteria for what was considered to be included and what was not. In the supplementary materials for this study, the newly defined criteria are broken down and discussed in detail. This brought to light the many dimensions of the problem that call for further investigation, as well as the breadth of the problem itself. After conducting research on a variety of different studies that followed a format that was comparable to this one, the author came to this conclusion. Only papers that satisfied all of the inclusion criteria were taken into consideration while carrying out the procedure of conducting a systematic review.

Because of this, the search was limited to locating just material that was pertinent to the inquiry. Research concepts that did not fulfill all of our evaluation criteria were not considered for consideration by our staff. As a consequence of this, it was made certain that a thorough investigation would be carried out. Because of this work, vital information regarding the research was uncovered, such as their names, authors, publication dates, locations, types of study activities, and parameters. The following is a list of the various product categories that are readily available. These are the kinds of skills that can be picked up via dedicated practice. This information might be provided in a number of different formats, depending on the source from which it was obtained.

Quality Assessment and Data Synthesis

Before deciding which papers to look into further, each author first carried out their own individual analysis of a separate piece of study that was described in the titles and abstracts of the publications. After that, we will read the totality of the publications that meet the inclusion criteria and are therefore suitable for inclusion in the systematic review.

Then, depending on our results, we will decide which papers should be included in the review. The pieces of writing that are going to be looked at have been chosen on the basis of these criteria. in order to make the process of picking articles for the evaluation as straightforward as possible. Which previous studies have been carried out, and what are the characteristics of those studies that make them suitable for inclusion in the review?

RESULT

Iramain, et al (2019)[9] conducted a studi with 103 children. They showed who fifty two children received MDI-SIB and 51 NEB-SIB. After the 4th hour, children on MDI-SIB had significantly ($P = 0.003$) lower rate of hospital admission than on NEB-SIB (5.8% vs 27.5%, RR: 0.21 [0.06-0.69], respectively). Similarly, a significant improved clinical score after 60 min and increase in oxygen saturation after 90 min of treatment was observed in MDI-SIB versus NEB-SIB group (4.46 ± 0.7 vs 5.76 ± 0.65, $P < 0.00001$; and 90.5 ± 1.7 vs $88.43\ 1 \pm 1$, $P < 0.00001$, respectively).

Papt, et al (2022)[10] showed incidence of severe asthma exacerbation was considerably reduced, by 26%, in the group that received the higher-dose combination in comparison to the group that received albuterol alone (hazard ratio = 0.74; 95% confidence interval [CI] = 0.62-0.89; $P = 0.001$). The hazard ratio (HR) for the lower-dose combination was 0.84 (95% CI = 0.71-1.00; $P = 0.052$) when compared to the hazard ratio for the albuterol-alone group. There was no discernible difference in the frequency of adverse events across the three trial groups.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Period	Therapy	Result
Iramain, 2019[9]	Paraguay	RCT	103 children (2-14 years of age) with severe asthma exacerbations	January 2013 to January 2017	NEB-SIB group received a 0.5% salbutamol aerosol solution (0.15 mg/kg weight, up to a maximum of 5 mg) in 5 mL of normal saline solution for 7 min every 20 min for 2 h, and then every 30 min for two more hours. Aerosol was generated by micro-nebulizer. MDI-SIB group received two puffs of salbutamol MDI (100 mcg/puff, Ventolin® GlaxoSmithKline) every 10 min for 2 h, and then every 30 min for two more hours.	Fifty two children received MDI-SIB and 51 NEB-SIB. After the 4th hour, children on MDI-SIB had significantly (P = 0.003) lower rate of hospital admission than on NEB-SIB (5.8% vs 27.5%, RR: 0.21 [0.06-0.69], respectively). Similarly, a significant improved clinical score after 60 min and increase in oxygen saturation after 90 min of treatment was observed in MDI-SIB versus NEB-SIB group (4.46 ± 0.7 vs 5.76 ± 0.65, P < 0.00001; and 90.5 ± 1.7 vs 88.43 1 ± 1, P < 0.00001, respectively).
Papi, 2022[12]	North America, South America, Europe, and South Africa	Multinational, phase 3, double-blind, randomized, event-driven trial	3,132 patients	No data	Fixed-dose combination (FDC) of 180 µg albuterol and 160 µg budesonide (each dose consisting 90 µg and 80 µg, respectively [higher-dose combination group]), FDC of 180 µg albuterol and 80 µg budesonide (each dose consisting of 90 µg and 40 µg, respectively [lower-dose combination group]), or 180 µg albuterol (with each dose consisting two actuations of 90 µg [albuterol-alone group]).	The higher-dose combination group had 26% less severe asthma exacerbation than the albuterol-alone group (hazard ratio [HR] = 0.74; 95% CI, 0.62 to 0.89; P = 0.001). Compared to albuterol-alone, the lower-dose combination group had a hazard ratio of 0.84 (95% CI = 0.71-1.00; P = 0.052). The three trial groups experienced similar adverse effects.
Ghimire, 2022[11]	India	Open-label randomized controlled trial	120 children (5-15 years of age) with poorly controlled asthma	No data	Azithromycin (10 mg/kg) three times weekly for 3 months	The numbers of children with well-controlled asthma according to GINA guidelines were 41/56 vs 10/56 in the azithromycin and control groups, respectively (P < .001). The median number of exacerbations requiring emergency visit and steroid use were fewer in the azithromycin group: 0 (interquartile range [IQR], 3) vs 1 [IQR, 6]; P < .001).
Amir, 2021[13]	Iraq	Comparative clinical study	100 children with poorly controlled asthma	January 2016 to January 2017	Salbutamol group (A) and Budesonide plus Salbutamol group (B)	After 30 minutes from ED admission, patients treated with a combination of budesonide plus salbutamol had significantly lower PISs (5.96±2.23) than those treated with salbutamol alone (7.32±2.18). At the end of 90 minutes, there were 28 (56 %) remaining patients in the ED from the salbutamol group and only 14 (28 %) patients from the combination group with a significant difference in the number of patients between groups (p<0.05). The mean duration of stay in ED had been significantly shorter in patients treated with nebulized budesonide plus salbutamol (p<0.05).
Wongwaree, 2022[14]	Thailand	Prospective, double-blind, randomized, controlled trial study	40 children (2 to 15 years old), with moderate to severe asthma exacerbation	December 1st, 2015 to January 31st, 2017	Albuterol in combination with budesonide (albuterol / budesonide 180 / 160 µg or 180 / 80 µg, two actuations of 90 / 80 µg or 90/40 µg, respectively) versus albuterol (180 µg, two actuations of 90 µg)	Nebulized magnesium sulfate was administered to sixteen patients, while ipratropium bromide and fenoterol was given to seventeen patients. Nearly all of the patients were categorized as having mild to moderate asthma attacks. There was not a statistically significant difference between the two study groups in practically any baseline parameter, including the PRAM score at 0 minutes, 30 minutes, 90 minutes, 120 minutes, or 240 minutes. Also, the amount of time spent in the hospital was comparable between the two groups (p = 0.83). There were no major incidents in either of the two groups.

Other study with 120 children (9.9 ± 3 years) showed the baseline parameters were similar between the groups. The numbers of children with well-controlled asthma according to GINA guidelines were 41 of 56 vs 10 of 56 in the azithromycin and control groups, respectively (P < .001). The median number of exacerbations requiring emergency visit and steroid use were fewer in the azithromycin group: 0 (interquartile range [IQR], 3) vs 1 [IQR, 6]; P < .001). No difference was found in Feno level, spirometry parameters, positive throat swab results, and adverse effects between the groups.[11]

From January 2016 to January 2017, a comparative clinical study was conducted at Karbala Teaching Hospital for children on patients aged 1 to 12 years who presented to the emergency department (ED) with mild to moderate asthma exacerbation. After 30 minutes from ED admission, patients treated with a combination of budesonide plus salbutamol had significantly lower pulmonary index score (PIS) (5.96 ± 2.23) than those treated with salbutamol alone (7.32 ± 2.18). At the end of 90 minutes, there were 28 (56 %) remaining patients in the ED from the salbutamol group and only 14 (28 %) patients from the combination group with a significant difference in the number of patients between groups (p<0.05). The mean duration of stay in ED had been significantly shorter in patients treated with nebulized budesonide plus salbutamol (p<0.05).[15]

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DISCUSSION

The Global Initiative for Asthma (GINA) defines asthma as a chronic inflammatory disorder of the airways in which many cells play a role, particularly mast cells, eosinophils, and T lymphocytes. Susceptible persons experience recurrent

episodes of wheezing, shortness of breath, chest tightness, and coughing, particularly at night or early in the morning. These symptoms are usually associated with widespread but variable airway obstruction, which is at least partially reversible both spontaneously and with treatment. The inflammation is also associated with airway hyperreactivity to various stimuli.[16,17]

Asthma is one of the most common major non-communicable diseases that has a major impact on quality of life. Asthma is ranked 16th among the leading causes of years living with disability and 28th among the leading causes of disease burden in the world. Asthma is the most common chronic disease among children worldwide. Approximately 339 million people (will increase to 100 million in 2025) have asthma and >80% of asthma-related deaths occur in low- and lower-middle-income countries.[18,19]

Wheezing, a high-pitched, whistling musical sound produced by airflow turbulence, is one of the most common symptoms. The mildest form is wheezing on final expiration. During the most severe episodes, wheezing is absent because of airflow limitation associated with airway narrowing and respiratory muscle fatigue. Chest X-ray is the initial imaging evaluation in most cases of asthma. Chest radiography is usually more useful in the initial diagnosis of bronchial asthma than in detecting exacerbations, although it is very valuable in excluding complications such as pneumonia. Most asthmatic patients have normal or hyperinflation chest radiographic findings.[16,17]

First randomized research shows that MDI and valved holding chamber administration of salbutamol and ipratropium bromide in children with severe asthma exacerbations reduced hospital admission (80%), clinical score, oxygen saturation, and tachycardia more than nebulizer administration.[9] Most guidelines and current evaluations indicate MDI salbutamol for moderate-severe asthma exacerbation, although nebulizers are recommended for severe acute asthma exacerbation when oxygen is needed. Hypoxemia requires nebulized oxygen. In severe acute asthma exacerbation, nasal cannula oxygen to the MDI-SIB was more efficacious than nebulizer oxygen. The increased pulmonary deposition of MDI/spacer may explain its superiority over nebulizer.[12]

Nebulizer-administered salbutamol and ipratropium caused more side effects in moderate-severe asthmatics than MDI. Our study also found that nebulizer-treated children with severe asthma exacerbation had a greater heart rate after 30 minutes than MDI-treated children. Nebulizers use more medication, oral pharyngeal deposit, and systemic absorption than MDI. In a recent metaanalysis treating adults/children with acute asthma in the ED or community, MDI beta-agonist had less side effects (eg, tremor, tachycardia, desaturations) than nebulizer.[20,21]

In another trial, which was carried out by Papi and colleagues (2022), the researchers utilized either FDC 180 g albuterol and 160 g budesonide (high dose), FDC 180 g albuterol and 80 g budesonide (low dose), or 180 g albuterol (albuterol-alone) as their treatment. Asthma clinical worsening increased trial drug use in all three study groups. Patients used 2 or fewer inhalations on most trial days (mean proportion of days with fewer than 2 inhalations: 53.7% in the higher-dose combination group, 52.6% in the lower-dose group, and 51.0% in the albuterol-alone group), while less than 2% used more than 8. The higher-dose combination group averaged 2.6 inhalations per day, the lower-dose group 2.7, and the albuterol-alone group 2.8, which is equivalent to 1.3, 1.3, and 1.4 doses of trial medicine per day.[10]

In children with asthma who were experiencing mild to moderate acute exacerbation, treatment with a combination of nebulized budesonide and salbutamol led to significant clinical improvement and a reduction in the length of time spent in the emergency department when compared to children who received nebulized salbutamol monotherapy.[15] The direct delivery of ICS into the airways allows for rapid action. ICS has been shown to be an effective and safe medication for long-term asthma control and has been recommended as first-line therapy for children with persistent asthma. However, there is insufficient clinical research data to determine whether ICS, in combination with inhaled SABA, can be used as first-line therapy for the management of acute asthma exacerbations.[22]

As we all know, beta2 agonists are the most effective relievers in the early stages of an asthma attack. However, in severe cases, this treatment is insufficient. The required additive anti-inflammation therapy, such as systemic corticosteroid, takes 4-6 hours to improve asthma outcome. As a result, GINA[16] guidelines recommend using ipratropium bromide, an anticholinergic, after salbutamol treatment fails. To treat patients with acute severe asthmatic attacks, we must use either ipratropium bromide / fenoterol or ipratropium bromide / salbutamol in our country. Ipratropium bromide/fenoterol is less expensive and easier to obtain than ipratropium bromide/salbutamol.[14,23]

A meta-analysis of systematic reviews found that MgSO4 treatment, both intravenous and nebulized, was effective in adults with asthma. However, in previous studies, children with acute asthmatic attacks did not fare as well with nebulized MgSO4 as they did with intravenous MgSO4. The MAGNETIC study argued that if we could treat patients within 6 hours of the onset of acute asthma, children with acute asthma would respond to nebulized MgSO4. To control severe acute asthma, nebulized MgSO4 was as effective as intravenous MgSO4. We confirmed the efficacy of nebulized MgSO4 in reducing the severity of acute asthma from the first hour of treatment in this study.[23]

The effectiveness of azithromycin in the treatment of severe asthma in adults has been demonstrated, and the antibiotic possesses both anti-inflammatory and immunomodulatory effects. Treatment with azithromycin over an extended period

of time at a low dose is recommended by current guidelines for the management of severe asthma.[24] A further advantage of azithromycin is that it is useful in the treatment of noneosinophilic asthma, a condition for which there are currently very few other therapeutic choices that show promise. Additionally, mycoplasma and chlamydial infections have been recorded in people with asthma that is not well managed.[13]

As a result, there is a possibility that anti-inflammatory drugs like azithromycin, which also works against atypical infections, could be useful. Concerns, such as the possibility of antimicrobial resistance, as well as potential side effects, such as cardiac, sensory, and gastrointestinal impacts, may prevent its broad use. Even if the current research did not find any cause for concern regarding the safety of azithromycin in children, it is nevertheless important that the safety of using azithromycin for extended periods of time be thoroughly and methodically investigated in large-scale investigations.[13,25]

CONCLUSION

Patients under the age of 18 who are experiencing acute exacerbations of their asthma may be prescribed beta2 agonist, azithromycin, inhaled corticosteroids, and antimuscarinics.

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