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Systematic Review of the Clinical Interventions for the Treatment of Asthmatic Children for Application in Saudi Arabia

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Abstract –

Background: Systematic Review of the Clinical Interventions for the Treatment of Asthmatic Children for Application in Saudi Arabia

Objective: The purpose of this systematic review of literature was to evaluate the efficacy of pharmacological and non-pharmacological interventions in helping develop the health standards for Asthmatic Children in Saudi Arabia as mentioned in the published studies.

Methods: To achieve the goal of this proposal for developing a systematic review, the bibliographic databases (including the Cochrane (CENTRAL), EMBASE PUBMED/MEDLINE and google scholar) were systematically searched for the studies related to health care system containing the data in the form of different analyses/ meta-analyses of RCTs (Randomized Control Trials). The search terms were combined with Boolean operators along with wild cards and truncations to broaden or narrow down the search results. Spelling variations (such as paediatric, paediatric) were also used to retrieve maximum relevant studies. The example search terms included: new-born* or youth* AND corticosteroid* or ICS* or steroid* or glucocorticoid* or cortico-steroid* or solumedrol or prednis* or dexamethasone or ormethylpred* or medrol or decadron or solucortef or mometoasone furoate* or triamcinolone acetonide* or fluticasone propionate* or beclometasone* or SABA or LABA or theophylline* AND leukotriene modifiers AND combination inhalers AND clinical intervention AND severe or acute or exacerbated AND asthmatic children or paediatric asthma AND treatment AND emergency department or emergency settings AND Saudi Arabia AND GINA criteria AND TRACK criteria AND C-ACT method.

Results: Of the final 30 studies, majority of the research findings focused on the asthmatic medications and their efficacy of treatment, whereas, the rest dealt with the current guidelines being implemented in Saudi Arabia worldwide and the context of their development. All the studies were then made part of the discussion where their clinical interventions and prevention programmes were discussed in detail and pharmacological and non-pharmacological treatment guidelines were established.

Conclusion: All reports and documents describing the clinical trials for Inhaled and Systemic Corticosteroids, Leukotriene Modifiers, Beta Agonists, Theophylline and Combination Therapies of multiple drugs from all over the world were evaluated for developing the most effective treatment guidelines for Asthmatic children from the time of their birth to the age of 16 years for application in Saudi Arabia.

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INTRODUCTION

According to the World Health Organization (WHO), Asthma is a non-communicable disease prevalent throughout the world, in some parts more than others; currently, approximately 235 million people are suffering from asthma globally, with asthma-related deaths most widespread in countries with

low per capita income (WHO, 2013). However, it is imperative to note that the prevalence of asthma is observed worldwide, regardless the extent of development or income earned in a country, although deaths are typically higher in less-developed or poorer countries; in fact, the prevalence of asthma is considerably high in urbanized or developed countries, due to which it is often referred to as the "disease of civilizations" (Kumar and Ghosh, 2009). Although both adults and children may fall victim to the disease, it is more frequently incurred by children (WHO, 2013). In the UK, asthma leads to roughly 1200 deaths per year; regardless of the growing awareness and treatment approaches, this statistic has remained largely stable in the last decade (Royal College of Physicians, 2014). Similarly, in other parts of the world, the number of deaths caused as a corollary of asthma has remained largely stagnant.

Although the treatment options for treating the various symptoms of asthma have improved to a large extent, people, especially children, are often admitted to hospitals for having acute flare-ups of asthma. In fact, many patients admitted to the emergency department in hospitals face aggravated asthmatic symptoms which they seek treatment for.

Pathophysiology of Asthma

Current research on the causes of asthma implies that a plethora of diverse environmental and genetic factors cause and contribute to the development of asthma. Some common causes include a family history of asthmatic cases, especially in first-degree relatives such as a mother, father, or sibling, premature birth, below average or extremely low birth weight, a high body mass index, which takes into account a person's weight and height, exposure to several materials such as tobacco smoke, or excessive occupational exposure to substances such as plastic, volatile chemicals and agricultural materials, and bottle feeding; all of these factors are known to cause and advance the development of asthmatic symptoms, for instance, bottle feeding evidently makes infants more susceptible to wheezing illness (Khachi, Meynell, and Murphy, 2014). Furthermore, several cultural changes and altered lifestyles of people living in more developed societies, where urban development is progressive, air pollution levels are often high, and infants are exposed to more hygienic living conditions, which typically diminish early exposure to allergens that can help prevent respiratory illnesses in adolescence, can also stimulate the development of asthmatic symptoms by serving as risk factors (Khachi, Meynell, and Murphy, 2014).

Asthma is considered a disease of "dysregulated immune system" in which the body's immune system produces a response against allergens (Kumar and Ghosh, 2009). Typically, most allergens, including components of tobacco smoke, plastics, paint, and agricultural substances, act as proteases or enzymes that break down proteins. In asthmatic patients, there is an over-production of various cells of the immune system, including mast cells, eosinophils, macrophages, and basophils and these cells commonly infiltrate the bronchial mucosa of cells of respiratory tracts, such as epithelial, endothelial, and smooth muscle cells; as a consequence of this massive invasion, disruption is causing in the respiratory tracts via widespread inflammation of the airways (Cohn, Elias, and Chupp, 2004). More specifically, the cytokine named interleukin-13, or IL-13, causes airway fibrosis by stimulating matrix metallo-proteases to act upon TGF-beta; this leads to eventual damage of the epithelium, smooth muscle layers, and fibroblast cells as gradually more and more cytokines, proteases, and chemokines are produced, all of which have a disruptive impact on the cells which constitute the respiratory tracts. Furthermore, the disrupted cells trigger the production of more IL-13, which enhances its damaging effect on the airways (Cohn, Elias, and Chupp, 2004). From the genetic viewpoint, individuals lacking microbial fauna lining the airways or who show a preference for the Th2 form of T-helper cells may are shown to be more likely to incur asthma. Hence the Th2 form, unlike the Th1 normal form, is a risk factor for asthma (Kumar and Ghosh, 2009). In fact, genome-wide screens have depicted that several chromosomal regions which harbor genes encoding numerous interleukins, including IL-13, IL-5, IL-9, IL-3, and IL-12b, are constantly multiplied or duplicated, and their gene products affect the development of T-helper cells, often causing them to adopt the Th2 phenotype or form (Bosse and Hudson, 2007; Vercelli, 2008). It is important to note, however, that these genetic factors act in conjunction with numerous environmental factors to make an individual more susceptible to developing asthma. Development of further gene discovery tools and more in-depth epidemiological studies are necessary to further widen the scope of asthma research and elucidate its causes to make treatment more appropriate and successful.

METHODOLOGY

This systematic review was stated earlier as building the treatment guidelines on the basis of clinical intervention conducted throughout the world for the treatment of acute asthma in the children up to the age of 16 years old since they are born in order to help establish recommendations and clinical guidelines for use in Saudi Arabia. First of all, it will be assessed and answered through a systematic review of literature available on the topic in the form of case studies and clinical data derived from all over the world on the asthma treatment and management.

This was primarily done through an electronic search to identify published studies, documents and reports containing the established guidelines in

PUBMED/MEDLINE, SCOPUS, and the Cochrane Library as database resources and other sources such as Google Scholar etc. They were filtered further using a set of inclusion and exclusion criteria to increase the relevance of consolidated data to the research.

INCLUSION AND EXCLUSION CRITERIA FOR DATA TYPES AND INTERVENTIONS

The inclusion criteria for this study was primarily to include publications describing the clinical and treatment data about acute asthmatic children from the time of their birth up to the age of 16 years, receiving treatment in the Emergency Department or any equivalent area for an acute asthmatic attack and the role of different asthma medications as highlighted above in the clinical interventions; and comparison between inhaled corticosteroids and systemic corticosteroids, improvement of lung function and relevant adverse effects were also considered. But studies containing both adult and pediatric participants' was also reviewed for guidelines and only pediatric asthma related data was taken from those studies to assess the problem at hand to a greater relevance. The studies describing the clinical data for treatment of asthma involving any form of medication for children specifically between the age group as defined earlier of 2 years and those describing treatment of asthma for adults or children more than 16 years was excluded in order to approach a more consolidated treatment for acute asthma. Furthermore, all studies describing the use of any of the corticosteroids (either oral, IM, IV, or inhaled) along with any adjuvant at ED or any acute care setting was considered in order to optimize the conclusion. Additionally, studies which are comparing two types of corticosteroids were also included for data extraction and the studies having data on corticosteroids treatment along with other co-interventions as additional regimens, such as anti-cholinergics, beta2-agonists, anti-histamines, theophylline compounds, etc. were also compiled for further association analyses. Furthermore, as The Saudi Initiative for Asthma 2014 outlines the criteria for outpatient management of asthma in children using the GINA criteria, The Respiratory and Asthma Control in Kids (TRACK) and the Childhood-Asthma-Control Test (C-ACT). These tests and criteria were also made part of the study in order to assess the severity of asthma symptoms in children before choosing the proper course of treatment with corticosteroids. Furthermore, as soon as the severity of asthma conditions had been analysed, pharmacotherapy was usually combined with the assessment in a stepwise approach in order to reach an optimal amount of medications and dosage. All the studies hence extracted were further filtered for having used English as the medium of language to increase the effectiveness of the research and all those mentioned in other languages were excluded from the data extracted.

DATABASE SEARCH STRATEGY

The studies related to health care system contain the data in the form of different analyses/ meta-analyses of RCTs (Randomized Control Trials). Thus the retrieval of all relevant data before devising the search strategy is as important as the quality of the search strategy itself. The whole data retrieved systematically was arranged according to the hierarchy of evidence which prioritizes them on the basis of research relevance.

The complete data analysis using specific parameters as defined later can also be used to highlight the areas of literature that can be handled through future research. The recommendations of 'The National Institute of Clinical Excellence (NICE)' state that a higher quality level can be achieved through a hierarchy of evidence. But there are some inherent limitations of hierarchy of evidence for performing qualitative research.

To achieve the goal of this proposal for developing a systematic review, the bibliographic databases (including the Cochrane (CENTRAL), EMBASE PUBMED/MEDLINE and google scholar) were systematically searched. The search terms were combined with Boolean operators along with wild cards and truncations to broaden or narrow down the search results. Spelling variations (such as pediatric, paediatric) were also used to retrieve maximum relevant studies. The example search terms included: new-born* or youth* AND corticosteroid* or ICS* or steroid* or glucocorticoid* or cortico-steroid* or solumedrol or prednis* or dexamethasone or ormethylpred* or medrol or decadron or solucortef or mometoasone furoate* or triamcinolone acetonide* or fluticasone propionate* or beclometasone* or SABA or LABA or theophylline* AND leukotriene modifiers AND combination inhalers AND clinical intervention AND severe or acute or exacerbated AND asthmatic children or paediatric asthma AND treatment AND emergency department or emergency settings AND Saudi Arabia AND GINA criteria AND TRACK criteria AND C-ACT method.

RESULTS

Asthma is one of the most common and quickly spreading chronic illness of childhood in Saudi Arabia and other countries in the world. The prevalence of asthma has dramatically increased from 8% to 23% in Saudi school children in a matter of 9 years according to a local survey in the country (Frayh et al., 2001). It is no doubt the leading cause of childhood morbidity and the global cost of treating and managing asthma goes beyond to become a socioeconomic burden for the families based on the medical treatments and medications. The purpose of this study is two-fold; primarily it seeks to understand the clinical and other

interventions conducted worldwide to help establish clinical guidelines for treatment and management of asthma in Saudi Arabia by way of systemic literature review and secondly, it seeks to also understand the extent and nature of acute asthma in children in Saudi Arabia and how it is being treated. The potential gaps and misunderstandings present in terms of knowledge or practice with respect to clinical and other interventions in the research conducted up till now in Saudi Arabia will be filled with research from the rest of the world. By the end of this systematic review, we were able to highlight the various recommendations and practices adopted for treatment of acute asthma in children from the time of their birth till the age of 16 years. The summary of the research findings have been displayed in a tabular form at the end of this section.

According to The Saudi Initiative for Asthma 2014 report, the management of asthma requires the collaborative effort of patients and their healthcare providers. Therefore, the strategy should consider the evolving research to adjust the pharmacotherapy methods for treating acute asthma patients. The main results achieved from the analysis of the reports included the new considerations for pharmacotherapy strategies and techniques in children which will be discussed as the important learning objective in conjunction with other research articles included in our literature review. Their benefits and harmful side-effects coupled with co-therapeutic approaches and dosage instructions will be made an important part of the analysis in order to help establish the guidelines for the ultimate asthma treatment and management.

As highlighted earlier, the main courses of treatment of asthma rely on using long-term modifications for the mitigation of asthma symptoms and help alleviate the chronic condition. They include inhaled corticosteroids, leukotriene modifiers, combination inhalers and theophylline amongst others. Inhaled corticosteroids remain to be one of the best options for the maintenance for childhood asthma as a monotherapy, however, the clinical benefits of ICS continue to remain controversial. Alangri in his research article highlights the various applications of corticosteroids in acute asthma conditions of patients and presents the current guidelines being employed in the treatment of asthma. In cases where patients have mild asthma exacerbation, the inhaled β2-agoists like albuterol (salbutamol) are sufficient for alleviating the symptoms and its dose can be repeated up to 3 times with the time interval of 15-20 minutes during the first hour of treatment. All these patients should further be treated with systemic corticosteroids at the recommended dose of 2mg/kg or 80 mg early in the treatment course as it will take about 4 hours to start working in the acute asthma patients and it also represents the maximum dosage. The R-enantiomer of albuterol, Levalbuterol has been scientifically claimed to be the effective form of the drug however the clinical trials have been unable to corroborate its efficacy over albuterol's. Patients who do not respond to albuterol should be then treated with systemic corticosteroids.

Furthermore, the current guidelines for the management of asthma also recommend using the inhaled β2-agoists in conjunction with anticholinergics for patients presenting acute severe or life threatening asthma symptoms in the emergency settings. They are generally administered through a nebulizer or a metered dose inhaler (MDI) containing a holding chamber, however, nebulizers are preferred for use in cases of acute or severe symptoms (Alangari 2014). As highlighted by Rodrigo et al., the data extracted from 32 randomized controlled trials showed that there were significant reductions in the hospital admissions in both children and adults when they were treated with inhaled anticholinergic agents. The combined treatment of these anticholinergic agents also proved effective in patients with severe asthma exacerbation and was able to produce a commendable increase in the spirometric parameters after 1 to 2 hours of treatment in both children and adults (Rodrigo et al., 2005). Qureshi et al were able to show that the anticholinergic medications such as Ipratropium bromide improve the pulmonary function of patients suffering from acute exacerbations of asthma. They conducted a randomized, double-blind, placebo-controlled study of 434 children who had acute asthma and were treated in the ED. They all received nebulized solution of albuterol (2.5 mg to 5 mg per dose depending on their body weight) thrice every 20 minutes according to the guidelines mentioned earlier. They also received an oral dose of corticosteroid (prednisone) with the second dose of albuterol. The children who went on to receive 500 microg (2.5 ml) of Ipratropium bromide with the second and third dose of albuterol were able to alleviate their acute condition and also showed reduced need for hospitalization (Qureshi et al., 1998). Zorc et al. also conducted a similar trial and concluded that the three doses of Ipratropium bromide led to an associated decrease in the reduction of treatment time for acute asthma patients (Zorc et al., 1999).

Inhaled corticosteroids have also been used in hospitals along with systemic corticosteroids for increasing the efficiency of acute asthma treatment. Rowe et al found that when 1600 mcg/day dose of budesonide was administered for 21 days, followed by 50 mg/day dose of prednisone for further 7 days as compared to the placebo treatment resulted in decreased relapse rate (Rowe et al., 1999). Even when Budesonide nebulization was added to systemic prednisolone in the treatment of acute asthma in children, as studied by Alangari et al., there was no substantial difference in the management of acute asthma symptoms or any effect on the admission rate of such patients in the ED (Alangari et al., 2014). However, another systemic review conducted by Edmonds et al of 12 trials also concluded that there

was no additional benefit of adding inhaled to systemic corticosteroids in reducing the relapse rate of acute asthma (Edmonds et al., 2012). Kramer et al on the other hand assessed the efficacy and the side-effects of Ciclesonide, a relatively new ICS, as compared to other ICS in the treatment and management of acute asthma in children. In their literature review, it was found that when ciclesonide was compared to budesonide in 1:2 ratio, the symptoms of asthma as well as the side effects were found to be similar, similar to when it was compared to fluticasone in 1:1 ratio. Therefore, the benefits as well as side effects could not be demonstrated by the test trials and demanded the need for longer-term superiority trials (Kramer et al., 2013).

Moving on, the review by Cates et al. looked at the combination therapy of formoterol and budesonide prevent in a single inhaler as a maintenance and reliever therapy against the use of inhaled steroids or ICS currently for chronic asthma conditions in adults and children. Amongst the 13 trials which included up to 224 children, they were able to find that the single inhaler therapy reduced the number of flare-ups that needed treatment with an oral steroid. However, there is also a contradictory evidence that the patients treated with high doses of inhaled steroids would even experience a flare-up and hence require any treatment with an oral steroid (Cates et al., 2013).

The uses of leukotriene modifiers and blocking leukotrienes all together were also studied in order to assess their effectivity in alleviating the acute asthma conditions in children since leukotrienes promote inflammation of the airways during the asthma to worsen the conditions of the patients. One of the leukotrienes, LTB4 (Leukotrienes B4) has been characterized as playing an essential role in the pathogenesis of asthma by Alzoghaibi et al. Upon the treatment of ICS and LABA, there is a corresponding decrease in the levels of the proinflammatory LTB4 resulting in the controlling of the inflammatory response of asthma in adults and children (Alzoghaibi et al., 2006). Therefore, it can be deduced that although the research remains inadequate and contradictory on the effectiveness of ICS, however, there is a decrease in the inflammation found in the patients and increase in the lung function. The effects of a leukotriene receptor antagonist, Montelukast, in children younger than 5 years of age with persistent asthma were studied by Knorr et al who developed the safety profile for the drug as well. Patients were give 4 mg of Montelukast and after 12 weeks of treatment with it, there was significant improvements in all the patients based on the multiple parameters of daytime/overnight asthma symptoms, the need for oral corticosteroids and peripheral blood eosinophils (which measured the level of inflammation due to asthma). Furthermore, the dose was also tolerated well by the patients aged between 2 to 5 years of age without the development of clinically adverse side effects including the severe exacerbation of asthma (Knorr et al., 2001). Moreover, Idrees et al studied the effects of adding Montelukast, a leukotriene modifier, in patients receiving the controller asthma therapies and the results were analysed 4 weeks after its administration. Despite the treatment with controller medications, the symptoms of mild to severe/acute asthma persisted in the patients, however, upon adding Montelukast, around 80% of patients reported improvement in their symptoms which was further found to be irrespective of the type of corticosteroid type or dose being given to the patients or LABA. The follow-up also showed around 92.2% of patients of feeling better on Montelukast (Idrees et al., 2007).

Furthermore, magnesium sulphate had also been shown to have bronchodilator effects and help in the management and treatment of acute asthma. A review of 16 trials conducted by Powell et al showed that the nebulised form of magnesium sulphate was when used with nebulised β2 agonist (with or without adding Ipratropium) however had no profound effect on the improvement of lung function and therefore is not recommended for the use of treating acute asthma (Powell et al., 2012).

Based on the research findings, the effectiveness and non-effectiveness of multiple asthma medications can be derived to establish guidelines for the treatment of asthma children in Saudi Arabia and are discussed in grave detail in the Discussion section.

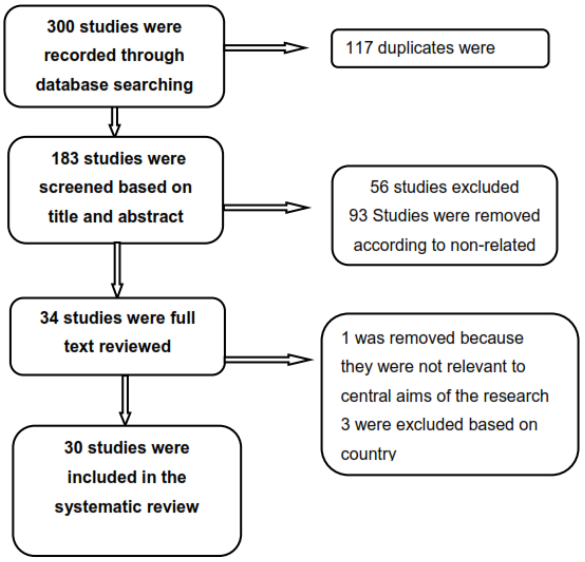

Figure 1: Selection process for the including articles in the systematic review

DISCUSSION

The wide research on asthma management and treatment worldwide helps to understand the gravity of the situation and the amount of persistent efforts that are required for continuous

development of the area in the underdeveloped or the developing countries of the world. Saudi Arabia has institutionalized multiple asthma management guidelines and programmes that are aimed at helping the exacerbations of asthma emergencies and mitigate the increasing trend of hospitalizations and severe medical conditions. The long term goals of asthma management are important to this research review as well as to all management studies because they help in identifying the key risk factors that need to be worked upon for the betterment of acute asthma conditions in children up to the age of 16 years. The main idea is that after the treatment of asthma, the patients should be able to control their symptoms of coughing, wheezing and shortness of breath adequately to put off the initiation of an asthmatic attack. Furthermore, they should be able to minimise their use of reliever therapies to almost less than 2 days a week. The normal pulmonary function should be maintained and there should be a corresponding increase in maintaining normal exercise and physical activity levels. Moreover, we should be able to prevent recurrent exacerbation of asthma and minimise the trip to Emergency Department or the need of hospitalizations. Minimum dosage of medications should be optimized that give greater asthma control, reduce mortality and increase the quality of life. Achievement of these goals would ultimately help in the successful management of asthma and its treatment.

Keeping these goals as our aim, this study strived to understand the available literature and devise guidelines that could help us in devising treatment methods and protocols for children with acute asthma at the time of their birth and persisting up till the age of 16 years. There are two possible paths from here, the pharmacological measures that can be taken to deal with the advent and exaggeration of the medical condition or the non-pharmacological measures to help control the symptoms and increase the quality of life for the patients. Both of these treatment methods should be used together to reach the optimum results and help in alleviating the acute asthma conditions in our patients. Therefore, highlighting both of the aspects of the treatment is very important for understanding the management of acute asthma in children and elevating their lifestyle.

Pharmacological Approach to the Management and Treatment of Acute Asthma:

The overall prevalence of acute asthma is highest amongst the children however there is little research available to establish best clinical practices based on the limited literature. Therefore, this area calls for a consolidated effort towards standardising the clinical practices that the hospitals all around the world have adopted for the effective management of acute asthma in children. Pharmacotherapy for childhood asthma has been described adequately in The Saudi Initiative for Asthma (SINA) guidelines 2014, Global Initiative for Asthma (GINA) guidelines, British Thoracic Society Guideline and other national guidelines. It targets the optimization of multiple asthma medications and therapeutic techniques to minimise the side-effects and largely increase the treatment and management of asthma. This review seeks to outline the recommendations aimed at and practical management and monitoring of asthma.

The first step towards any disease treatment is the differential diagnosis that tells you the exact condition of the patient and the medications that will be the most effective in such a situation. Therefore, in childhood asthma, a list of questions can be prepared for the correct diagnosis of asthma for effective treatment and these can include, but not limited to, questions regarding asthma symptoms of wheezing and cough, the specific triggers that might have initiated the attack (for example passive smoke, cold air exposure, infections, pets, humidity etc.), any altered sleep patterns and daytime/night-time cough or wheezing, exacerbations that might have happened in the preceding months/years and any nasal symptoms (itching, sneezing etc.). In infants, who are younger than 2 years, noisy breathing, sucking in of the chest (retractions), any changes in the respiratory rate and difficulty with feeding can serve as the indications for acute/severe asthma progression. On the other hand, shortness of breath during the day or night, fatigue, repeated complaints about illness and poor school performance can serve as the indicators for children older than 2 years of age. Multiple tests can be carried out to further validate the diagnosis of asthma and its severity in patients. The most common techniques is the chest X-ray which is usually performed at the first visit. Furthermore, Peak Expiratory Flow (PEF) and forced expiratory flow-volume loop can also be used for lung function measures and identifying any obstruction for classifying the severity of asthma.

After the diagnosis of the severity of asthma, treatment should be administered in a step-wise approach based on the severity, persistence and frequency of symptoms. It is highly possible that not all children will respond to the same therapies and the children should be monitored closely to understand the efficacy of any one approach.

The asthma medications that are currently being used worldwide have been highlighted earlier and include reliever and controller medications. In cases of cute asthma management, these medications are used either in solitude or in conjunction to help with the asthma symptoms and bring about a positive change in the lifestyle of the patients. Multiple guidelines can hence be established for advising and usage of these medications in the hospitals along with the step-wise protocol of treatment of acute asthma.

Treatment Guidelines:

The management of severe and acute asthma in the age group of 0-2 years is problematic because of the difficulties faced initially in the diagnosis and then in advising the correct course of treatment since there are controversial literature present on the different medications we have outlined here in this review. For example, there is evidence for the benefit of β2-agonist therapy in this age group as well as literature available that prove that this therapy has no profound effect on the treatment of severe asthma. However, based on the national guidelines presented to us from our literature survey of research articles from all over the world, we can optimize our clinical practices to treat asthma in children of 0-2 years of age based on the following protocol.

Table 1: Protocol for pharmacological treatment of Asthma in Children of 0-2 years of age

1. Diagnose Asthma if there have been greater than 3 episodes of reversible bronchial obstruction in the time period of 6 months.
2. Begin treatment with intermittent B2 agonists – nebulized or oral.
3. To control viral wheezing, treat with LTRA daily controller therapy. Proceed to advise as the short-term or long-term treatment based on the examination of symptoms and severity of asthma.
4. In cases of persistent asthma or incidence of acute asthma, administer nebulized or inhaled oral corticosteroids as daily controller therapy.
5. Administer oral corticosteroids for acute and obstructive episodes for the period of 3 -5 days in the dosage of 1-2mg/kg (for example, prednisone).

Table 2: Protocol for pharmacological treatment of Asthma in Children older than and of 2 years of age

1. Administer ICS (in dosage equivalent to 200 µg BDP) OR LTRA (dosage according to the age)*
2. In case of insufficient control, increase ICS dose to 400 µg BDP equivalent OR add ICS to LTRA.
3. Step down treatment if appropriate after the control of asthma attack or in cases of no further exacerbations.
4. In case of insufficient control, check for allergen avoidance and re-evaluate diagnosis.
5. If correctly diagnosed with asthma, proceed to increasing ICS dose to 800 µg BDP equivalent OR add LTRA to ICS OR add LABA.
6. Step down treatment if appropriate after the control of asthma attack or in cases of no further exacerbations.
7. In case of insufficient control, proceed to considering Theophylline and Oral corticosteroids for effective treatment.

*one of the two

Table 3: Protocol for pharmacological treatment of Asthma in Children of 3 – 5 years of age

1. Administer ICS, budesonide 100 – 200 µg x 2 or fluticasone 50 – 125 µg x 2 using Metered Dose Inhaler (MDI).
2. Administer 1 – 2 puffs of short-acting β2-agonists, salbutamol 0.1 mg/dose or terbutaline 0.25 mg/dose at 4 hours interval or as needed by the patient.
3. Monotherapy through LTRA instead of ICS if the symptoms are intermittent or persistent.
4. In case of insufficient control with ICS, add Montelukast (LTRA) 4 mg granules or 4 mg chewing tablet.
5. In case of insufficient control, add LABA OR increase ICS dose (as recommended by the physician) OR add Theophylline.

Furthermore, treatment with LABA for the children of ages 3 – 5 years in case of worsening of asthma symptoms has no published evidence, however, can be used if all the other options do not help in alleviating the condition of the patient.

Treatment of severe asthma uses the amalgamation of several medications and specific guidelines to improve the condition of the patients. Inhaled short-acting β2-agonists are the first-line of treatment for acute asthma in children who are 2 years old and over. In cases where they are needed after every four hours or less, long-acting β2-agonists should be discontinues and they should be administered with an MDI and a spacer. In order to administer ICS or β2-agonists, the preferable mode of delivery is an MDI with a spacer or a DPI instead of using a nebulizer. However, for children under 4-5 years of age there are

complications in using these techniques and therefore they must rely on nebulizers and MDIs that contain a chamber for drug delivery.

Nebulizers can be used for all ages and they supply drug through tidal breathing. On the other hand, pressurized MDI or metered dose inhaler can be used for children up to the age of 7 years with various inhalation techniques of using tidal breathing with face mask or mouthpiece. Therefore, in children with acute or severe asthma, frequent doses of β2-agonists should be administered. Moving on, repeated doses of Ipratropium bromide should be administered early to treat the children who end up responding poorly to the β2-agonists. They are combined to the β2-agonist solution and used for the first few hours of admission before being weaned or discontinued. Steroid therapy can also be used early in the treatment of acute asthma and oral prednisolone is generally the choice for children except for cases where the patients are unable to bear the dosage. There is also lacking evidence for using ICS instead of oral steroids in cases of acute asthma attacks therefore they should not be used. They are recommended for use as normal maintenance therapies in children. The stepwise protocol for the management of acute asthma episodes in children can also be summarised as follows:

1. Administer 2 to 4 puffs of Inhaled short-acting β2-agonists (for example, 200 µg of salbutamol) after very 10 – 20 minutes in 1 hour.

2. In case of insufficient control, administer nebulized form of β2-agonists (2.5-5 mg of salbutamol) after every 20 – 30 minutes. Ipratropium bromide can also be mixed with the β2-agonists solution at 250 µg/dose and again administered after every 20 – 30 minutes.

3. Simultaneously, the high-flow oxygen should be maintained to ensure normal oxygenation.

4. In cases of persistence of symptoms, administer oral or I.V steroids. They both are found to be of similar efficacy, however, the tablets are preffered to inhaled steroids and a dose of 1-2mg/kg of prednisone or prednisolone should be administered. This course of treatment should be advised for 3 days, which should alleviate the symptoms and maintain the exacerbations.

5. In case of insufficient control, β2-agonists can be administered intravenously. Early addition of I.V Salbutamol in the dosage 15 µg/dose followed by infusion of 0.2 µg/kg/min is found to be efficient in alleviating the severe asthma condition.

6. In case of insufficient control, proceed to hospitalizing the children in ICU and advise administration of aminophylline in situations of life-threating bronchospasm with maximum dosage of bronchodilators and steroid tablets.

The dosage can be optimized to 6mg/kg to be given after every 20 minutes with continuous ECG monitoring and I.V dosing.

Physicians can also consider adding 150 mg of magnesium sulphate to the nebulised solutions of salbutamol and ipratropium bromide in the first hour in children for a short duration of acute asthma attack and who also have oxygen saturation less than 92%.

Non-pharmacological Approach to the Management and Treatment of Acute Asthma:

There needs to be an increase in creating parental and otherwise awareness on the management of asthma symptoms and to help understand the various risk factors associated with the progression of disease. Therefore, the simple treatment with medications is not to be deemed as necessary and rather there needs to be an increased association between the doctors, patients/children and their parents for helping with the treatment of the disease. Self-management educational programmes have been shown to be successful for children under 5 years of age or between 7 to 14 years of age.

These educational programmes can be designed to include various learning workshops on the pathophysiology of asthma, how it is triggered and how the symptoms can be made better through breathing exercises or early dosage of medicines at home, without the need of having to rush the children to hospital every time their condition worsens. Furthermore, there need to training workshops on the medications being administered, their correct dosage and which medications to use in case of emergencies. So that the parents can help the doctors in being better aware of their children's treatment protocols and assisting the doctor in taking care of the well-being of the patient. They can be shown asthma videos, games and interactive programs or illustrated books to ease their process of learning. Furthermore, there need to be planned educational strategies on educating parents on the benefits and side-effects of all the therapies that are being considered for their children so that they can make an intelligent decision and are cautious enough to look out for the side-effects and reach a timely treatment for them.

The children on the other hand children can also be made to participate in these interactive sessions and made to watch videos and interactive games that can help them in understanding the role of

various medications they are taking and what steps should they take if they feel their asthma is getting worse. There should be increasing trend of support groups or interactive platforms through which families can get-together and support each other through their children's medical treatment and share their experiences with various therapeutic methods and techniques.

Saudi Arabia currently lacks the establishment of these non-pharmacological approaches to managing the acute asthma incidences in its country and helping the families in understanding the disease better and supporting their children. Although, it has strived to optimize its clinical practices up to the top-notch, however, it needs to also provide avenues to its patients and their families to better complement the doctors and physicians and make educated decisions about the lifestyle of their children.

CONCLUSION

Exacerbation of Acute Asthma in children has been an increasing concern for physicians in Saudi Arabia since ED admissions have been ever increasing. The interventions and treatment guidelines need to be revised in order to alleviate their symptoms and improve their health standards. For this purpose, a systematic literature review was carried out of the treatment guidelines established worldwide in order to help recommend changes to the guidelines being followed in Saudi Arabia. During the course of this study we were able to realise two important constituents of the effective management of Asthma that needs to be developed in Saudi Arabia. Primarily, there needs to be focus on the improvement of non-pharmacological interventions and programmes to educate the children and their families about the pathophysiology of Asthma and support their children during the prolonged treatments. Furthermore dietary concerns of the children also need to be adequately demonstrated to the families. Such support groups and awareness sessions are not present in Saudi Arabia and therefore need to be develop for increasing the interaction between the parents and the physicians so that they can together contribute towards the health of the children. On the second level, the efficacy of ICS have been realized through the wide literature reviewed during the course of the study and therefore their use in conjunction with the other medications including leukotriene modifiers, beta agonists, theophylline and combination therapies need to be standardized, much like they are being done currently. However, improvements have been suggested based on the evidence of research as found in this review that can bring about a positive change in the ED admissions and help alleviating the episodes of acute asthmatic attacks in children and improving their health standards.

LIMITATIONS

Limitations of the current proposed study will be same as those usually associated with all systematic reviews. One of the most important phenomena is the heterogeneity and a broader range of quality of the original articles besides facing the complication of extracting data in languages other than English and where the original articles could not be made available for further analyses. Studies usually utilise a much wider range of interventions and their combinations, study population, and outcome variables. Therefore such explanations for different interventions are difficult to explain based on EPOC criteria to account for heterogeneity of data.

The studies utilised as data extraction sources are often accompanied with unclear intensity of the interventions and the publication bias cannot be managed easily. Subsequently, the efficacy of mixtures of interventions may seem to be too positive.

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