Acta Scientific PAEDIATRICS (ISSN: 2581-883X)

Volume 4 Issue 6 June 2021

Review Article

Recent Approaches in the Management of Difficult to Treat Asthma in Pediatric Population - A Brief Review

Edwin Dias[1,2]* and Shwetha N[3]

[1]Professor and Head, Department of Pediatrics, Srinivas Institute of Medical Sciences and Research Centre, Mangalore, Karnataka State, India

[2]Adjunct Research Professor, College of Allied Health Sciences, Srinivas University, Mangalore, India

[3]Final Year Pharm D., Srinivas College of Pharmacy, Valachil, Mangalore, Karnataka State, India

***Corresponding Author:** Edwin Dias, Professor and Head, Department of Pediatrics, Srinivas Institute of Medical Sciences and Research Centre, Mangalore, Karnataka State, India.

Received: April 26, 2021

Published: May 15, 2021

Abstract

Introduction: Pediatric patients with difficult-to-treat asthma experience a heavy burden of exacerbations, symptoms, therapeutic failure, adverse drug reactions, and increased health care costs. Frequent cough, dyspnoea, chest tightness, and wheeze interfere with normal daily activities, sleeping, overall quality of life, and education of children. Difficult-to-treat asthma affects a small group of children with asthma but represents a challenging mix of misdiagnosis or incorrect diagnosis, multiple co-morbidities, severe airway pathophysiology, inadequate self-management, and treatment complications. Thus management of such cases requires beyond pharmacotherapy of asthma because patient-related and disease-related domains need to be considered first. Therefore, prevention of asthma exacerbations is an essential goal in difficult-to-treat asthma therapy and requires more focused individualized treatment that involves the elimination of risk factors, treatment of co-morbidities, treatment with anti-asthmatics, and improving medication adherence.

Methodology: A brief review of all the relevant standard articles was conducted.

Result: The study involved a brief review on assessment of risk factors in the pediatric population with difficult-to-treat asthma and pharmacological management i.e. optimal use of long-acting muscarinic antagonist (tiotropium), and biological monoclonal antibody treatment (Omalizumab, Mepolizumab, Dupilumab, and Benralizumab) which were found to be safe and effective in the pediatric population.

Conclusion: Management of difficult-to-treat asthma in the pediatric population requires the elimination of modifiable risk factors, treatment of co-morbidities, and treatment of exacerbations with newer agents which were found to be effective in reducing hospitalizations and frequent Emergency Department visits. Thus individualized treatment must be preferred in these patients.

Keywords: Difficult-to-Treat Asthma; Pediatrics; Risk Factors; Recent Approaches; Management

Abbreviations

A list of abbreviations are mentioned in the following table 1.

Sl. no.	Abbreviations	Full form
1	WHO	World Health Organisation
2	DALYs	Disability Adjusted Life Years
3	ICS	Inhaled Corticosteroids
4	GINA	Global Initiative for Asthma
6	OCS	Oral Corticosteroids
7	CDC	Centers for Disease Control and Prevention
8	GERD	Gastro-Oesophageal Reflux Disease
9	OSA	Obstructive Sleep Apnoea
10	VCD	Vocal Cord Dysfunction
11	CF	Cystic Fibrosis
12	PCD	Primary Ciliary Dyskinesia
13	CT	Computed Tomography
14	NO	Nitric Oxide
15	BAL	Bronchoalveolar lavage
16	MDIs	Metered-Dose Inhalers
17	FEV	Forced Expiratory Volume
18	SABAs	Short-Acting Beta Agonists
19	ED	Emergency Department
20	NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
21	CRS	Chronic Rhino-Sinusitis
22	LABA	Long-Acting Beta-2 Agonists
23	LTRA	Leukotriene Receptor Antagonists
24	IgE	Immunoglobulin E
25	LAMA	Long Acting Muscarinic Antagonists

Table 1: List of abbreviations used in this study.

Introduction

Asthma is a multi-factorial and complex chronic inflammatory disease of the airways characterized by reversible airflow obstruction and airway hyper-responsiveness [1,2]. This is one of the major non-communicable diseases that affected more than 339 million people globally as per the Global Burden of Disease Study 2016 [3]. As per a systematic study conducted by the World Health Organisation (WHO), there were 417,918 deaths due to asthma at the global level and 24.8 million Disability Adjusted Life Years (DALYs) attributable to Asthma in 2016 [4].

Most of the children diagnosed with asthma achieve optimal symptom control when treated with low-to-medium doses (<500 mcg/day fluticasone equivalents) of inhaled corticosteroids (ICS) [5]. But in case of difficult to treat asthma where asthma is still uncontrolled despite GINA (Global Initiative for Asthma) Step 4 or 5 treatments (e.g. medium or high dose inhaled corticosteroids (ICS) with a second controller i.e. maintenance Oral Corticosteroids (OCS)), or that requires such treatment to maintain good symptom control and minimize the risk of exacerbations. It does not mean a 'difficult patient', rather it just means 'difficult-to treat' because of modifiable risk factors such as incorrect diagnosis, incorrect inhaler techniques, non-compliance, psychological factors, environmental factors or any other co-morbidities [6,7].

Prevalence of difficult-to-treat asthma in children

Childhood asthma is the most common worldwide disease, imposing a huge burden on the patient, their family, as well as society, include decreased quality of life for the patient and their family, as well as high costs for society [8]. In developed countries, the healthcare expenditures for asthma are 1-2% of the total healthcare costs [8].

As per the report of Centers for Disease Control and Prevention (CDC) 2016, the prevalence of asthma in children aged 5 to 11 years and 12 to 17 years is 9.6% and 10.5% respectively with an overall prevalence of asthma in children under 18 years old in the US is reported as 8.3% [9]. According to an observational, cross-sectional, two-phase, multicentre study conducted in 30 hospitals in Spain by Plaza-Martín AM and team the prevalence of difficult-to-treat asthma was 24.2% among12,376 asthmatic children [10].

Risk factors and reasons for the frequent exacerbations in difficult-to-treat asthma

Recurrent exacerbations are one of the major causes of morbidity and medical expenditure in patients with difficult-to-treat asthma [10]. In the majority of pediatric patients, asthma can be well controlled with the help of simple regimens of inhaled drugs. But, some patients with difficult-to-treat asthma suffer from frequent exacerbations of asthma resulting in days of absence from school, the need for emergency care or hospitalization [11,12].

In difficult-to-treat asthma, optimal symptom control cannot be achieved due to several factors that are independent of the disease such as incorrect diagnosis, multiple co-morbidities, poor medication adherence, poor inhalation techniques, psychological or environmental factors [13,14].

Incorrect diagnosis

It is very essential to remember that "all wheezes are not the symptoms of asthma". According to a study, in 12-30% of cases, "uncontrolled asthma" was another condition, which was misdiagnosed [15]. Most conditions that may be mistaken for asthma are congestive heart failure, GERD (Gastro-oesophageal reflux disease) obstructive sleep apnoea (OSA), or vocal cord dysfunction (VCD) many others [16,17].

When there is a lack of response to standard therapy, the diagnosis of asthma must be enquired. If asthma control is difficult to achieve, differential diagnostics of conditions with symptoms that may be similar to those of asthma should be intensified. Clinical criteria and differential diagnosis in children with wheezing are described in table 2 and 3 [17].

Poor medication adherence

Once the diagnosis of asthma is confirmed, it is important to ensure adherence to the medication regimen as non-compliance is one of the major problems impairing achievement of the optimal asthma control in children [14,16]. In children with difficult to treat asthma this is particularly necessary because non-adherence to medication is a confounding factor which is responsible for poor clinical outcome [18]. According to a study, 10 to 46% pediatric population diagnosed with asthma were poor adherent to medications and even more so with Metered-Dose Inhalers (MDIs) compared with oral medications [19]. As per one more study, low-compliant patient had significantly worse lung function parameters (post-bronchodilator FEV1 75.4 vs. 84.3, $p < 0.05$), higher chances of ventilation disorders due to asthma (19.2% vs 2.6%, $p < 0.05$) and more sputum eosinophil counts (0.66% vs. 0.54%, $p = 0.05$) [20].

Possible alternative diagnosis	The clinical condition of the pediatric population that is attributable to diagnoses
	Perinatal and family history
Primary Ciliary Dyskinesia and Cystic Fibrosis and Chronic Lung Disease of Prematurity.	Symptoms present from birth itself
Neuromuscular disorders, Primary Ciliary Dyskinesia and Cystic Fibrosis (CF)	Family history of unexplained chest disease
Primary Ciliary Dyskinesia (PCD)	Serious upper respiratory tract disease
	Signs and symptoms
Bronchiectasis, Recurrent aspiration, Primary Ciliary Dyskinesia, Protracted Bacterial Bronchitis, and Cystic Fibrosis	Persistent moist cough
Gastro-Oesophageal Reflux Disease (with/without aspiration)	Excessive vomiting
Problems associated with swallowing (with/without aspiration)	Dysphagia
Breathing Dysfunction, Panic attacks	Breathlessness associated with lightheadedness and peripheral tingling
Disorders of Trachea or Larynx	Inspiratory stridor
Problems of Larynx	Abnormal voice or cry
Developmental Anomaly, Foreign Body, Post-infective syndrome	Focal signs in chest
Extrinsic intrathoracic airway compression, Foreign Body Airway-malacia, Luminal obstruction, and Cystic Fibrosis	Persistent wheeze
Bronchiectasis, Cystic Fibrosis	Finger clubbing
Gastro-Oesophageal Reflux Disease (GERD), Cystic Fibrosis	Failure to thrive

Table 2: Clinical conditions need to be evaluated to avoid incorrect diagnoses in children with wheezing.

Time for high index suspicion	Necessary diagnostic procedures	Possible alternative diagnosis
Daily productive cough with sputum, malabsorption, clubbing, and failure to thrive, frequent chest infections, and airways bacterial colonization	Sweat chloride test, Genetic tests, Swab culture, Lung Function tests, Chest Computed Tomography (CT)	Cystic fibrosis and bronchiectasis
Recurrent airway infections, Systemic infections (from a few months of age)	Immunoglobulins and specific tests	Immunodeficiency
Neonatal Upper Airway Symptoms, Chronic Rhinosinusitis, Daily Wet Cough, Laterality Defects, and Recurrent Otitis Media,	Nasal Nitric Oxide (NO), Genetic tests, Immunofluorescence, Chest Computed Tomography(CT) Electron Microscopy, and High-Speed Video Microscopy	Primary Ciliary Dyskinesia (PCD)
Chronic wet cough, Good response to a prolonged course of antibiotics but poor response to beta-2 agonists	In many cases no need for examinations, Swab culture, Bronchoscopy with Bronchoalveolar lavage (BAL)	Protracted Bacterial Bronchitis
Monophonic wheeze even if the child is active, High-risk setting (i.e., patient operated for a vascular ring or tracheo-oesophageal fistula), Presence of associated stridor	Lung function test (truncated expiratory flow in spirometry), Dynamic Computed Tomography (CT), and Flexible bronchoscopy	Airway malacia
History of choking, Abrupt onset of symptoms, , Focal hyperinflation of lung or Unilateral monophonic wheeze	Bronchoscopy, chest x-ray	Airway foreign body
Prolonged dry, honking cough; Absence of cough while sleeping; Absence of any other physical findings	Medical investigations should be avoided	Habit cough
Absence of structural abnormalities, Sudden worsening of asthma symptoms, and no response to asthma medications	Video of an attack, Laryngoscopy is recommended during an attack	Vocal cord dysfunction (VCD)
Previous history of severe viral respiratory infection especially in the first 3 years of life	Computed tomography scan (characteristic air trapping and mosaic pattern)	Bronchiolitis obliterans

Table 3: Time for high index suspicion for differential diagnosis in children with wheezing.

Several reasons exist for poor medication adherence in children and adolescents including complex treatment regimen (difficulties in using an inhaler, multiple inhalations per day, and use of several different types of inhaler), unintentional factors (such as being forgetfulness, absence of a daily routine), and intentional factors (wrong perception that treatment is not necessary, denial, embarrassment, inconvenience, fear of side effects, treatment cost and laziness) [21].

Sometimes, if the patients are compliant, the use of improper inhaler techniques may prevent the appropriate delivery of the drug. Not only this, incorrect inhalation technique could increase the risk of both disease exacerbations as well as the adverse effects of treatment [22]. It is estimated that most of the patients diagnosed with asthma (up to 70-80%) incorrectly use their inhalers and are not aware of the errors they make [14]. These types of activities not only hinder the drug to reach steady-state concentration but also prevent the achievement of optimal clinical outcomes.

Psychosocial factors

Even though many pediatric patients diagnosed with asthma function well, it has been observed that some of them have a higher risk of internalizing emotional and behavioural problems such as anxiety and depressive symptoms [23,24]. This disease burden may lead to behavioural problems such as difficulties in separation or individuation from parents and concomitant anxiety [24]. These psychosocial factors not only trigger the exacerbation of asthma through neuro- endocrine and immune mechanisms, but also may lead to poor adherence, poor disease control and asthma management, and poor functional health status [25,26].

Patients diagnosed with asthma and co-morbid depressions are very difficult to treat. Hence, it is necessary to address and treat the depression before there can be any success with asthma therapy for this population [27].

Parenting stress

Parents play a crucial role in the social, autonomy, and overall development of their children. When parents establish a caring, supportive and positive environment, this will have a positive impact on developmental outcomes for especially children growing up with a disease [28].

Some studies have indicated that parental stress is one of the potential cause and consequence of disease activity, asthma control and quality of life, and behavioral problems in children and can exert an influence on the disease through poor treatment adherence or worsening of the patient condition (through physiological stress response systems such as the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis) as to compliance with asthma management still largely depends upon caregivers in children [29-33].

Environmental factors

For children with difficult-to-control asthma exposure to allergens or other triggers can exacerbate the clinical signs and symptoms of asthma. Along with pollens, cold conditions, and dust mites, microbial volatile organic compounds released from excess indoor mold growth and water-intruded areas are also increasingly being recognized as important irritants triggering asthma [34]. Thus identifying and eliminating these factors may help with asthma management [16].

Regular or over-use of SABAs (Short-Acting Beta Agonists)

Frequent and overuse of SABAs causes down-regulation of beta receptors and lack of response leading in turn to greater use [35]. Sometimes overuse may also be habitual. A study revealed that dispensing of more than 3 canisters per year i.e. average of 1.5 puffs per day or more is associated with increased risk of hospitalization or Emergency Department (ED) visits independent of the severity [36]. One more study revealed that dispensing of more than 12 canisters per year (once a month) increases the risk of death [37].

Other factors

Several other factors such as concomitant diseases (GERD, obesity, allergic rhinitis or chronic rhino-sinusitis, etc), poor socio-economic conditions, and drug history of nonsteroidal anti-inflammatory drugs (NSAIDs) and β-blockers can be significant unidentified precipitators of difficult to treat asthma [38,39].

Discussion

Difficult-to-treat asthma can be defined when asthma is not controlled despite GINA step 4 or 5 treatment [6]. During the management of difficult to treat asthma, certain factors must be evaluated: [40].

Factors to be evaluated before starting the actual treatment of difficult-to-treat asthma

- Confirmation of diagnosis;
- Correction of modifiable risk factors;
- Controlling co-morbidities.

Confirmation of diagnosis

The diagnosis of asthma should be confirmed based on the clinical history of the patient and relevant tests before diagnosing difficult to treat asthma [40]. The differential diagnostic tests must be performed to prevent incorrect diagnosis as described in table 2 and 3.

Correction of modifiable risk factors

Risk factors that could be modified should be corrected before managing difficult to treat asthma. Modifiable risk factors include incorrect inhaler techniques, smoking (even secondary), poor medication adherence, and environmental factors such as allergens, pollens, or non-specific stimuli.

Controlling co-morbidities

Co-morbidities must be controlled well before initiating the actual treatment of difficult-to-treat asthma. Common co-morbidities associated with difficult to treat asthma include chronic rhino-sinusitis (CRS), GERD, obstructive sleep apnoea (OSA), obesity, and depression/anxiety disorder. Controlling these co-morbidities can help in the optimization of treatment as concomitant co-morbidity can affect diagnosis, reduce positive therapeutic outcomes, in-

crease acute exacerbation, and result in patients receiving excessive treatment.

Management of difficult to treat asthma

Non-pharmacological interventions:

Management of patients diagnosed with difficult-to-treat asthma extends beyond asthma pharmacotherapy because multiple patient-related, as well as health status-related factors, need to be addressed before initiating the actual treatment [41].

Patient education is necessary for the management of difficult-to-treat asthma. Lack of information about disease, drugs, and lifestyle modifications may lead to poor clinical outcomes. To ensure better disease control, patients with difficult-to-treat asthma and their family need to understand the nature of the disease, signs and symptoms, time of exacerbations, treatment principles, the importance of regular use of asthma medications, avoidance of risk factors or asthma trigger factors, and self-management of asthma [41]. A study revealed that patients who received training on inhalation techniques made significantly fewer errors while using their inhalers ($p < 0.0001$) [42]. On the other hand, patients who received no instructions were more likely to report frequent exacerbations of asthma than those who received instructions on inhalation techniques by a healthcare provider [43,44].

Pharmacological interventions

The use of Inhaled corticosteroids (ICS) with long-acting β2 agonists (LABA) as a combination is a mainstay of asthma treatment. In patients who do not achieve good symptomatic control or optimal clinical outcomes with the use of a medium-dose ICS-LABA combination (GINA step 4), it is recommended that the dose of ICS (a high-dose ICS-LABA combination) must be increased or a second controller agent, such as tiotropium or leukotriene receptor antagonists (LTRA), can also be added. Before moving to GINA step 5 treatment, maintenance and reliever therapy with an Inhaled Corticosteroids (ICS) with a LABA i.e. formoterol combination can be considered. The management of step 4 and step 5 of asthma is described in figure 1 [40].

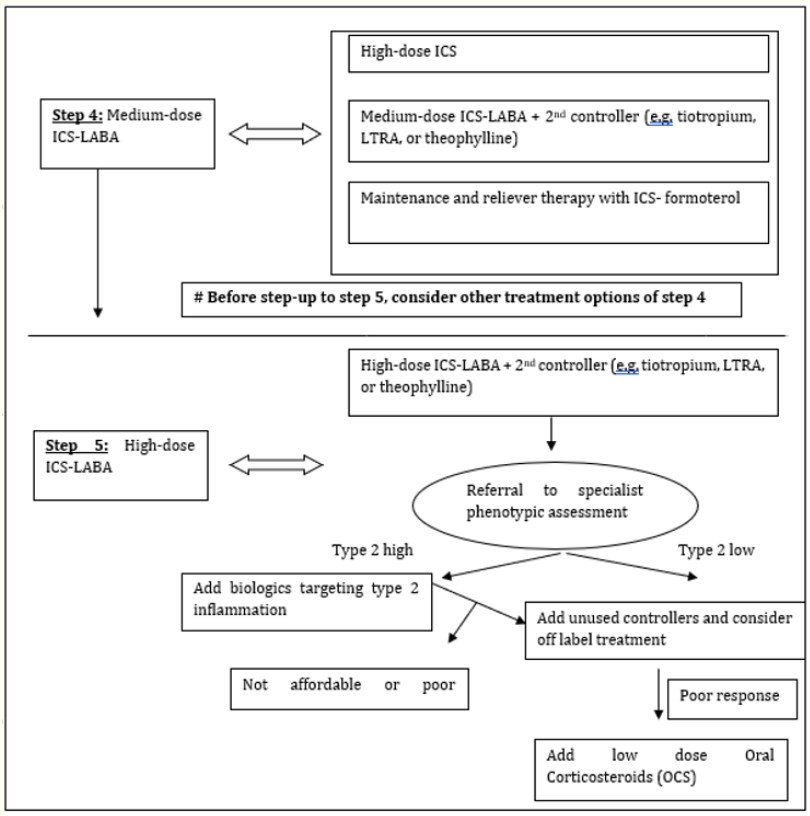

Figure 1: Management of step 4 and step 5 of asthma.

Patients with uncontrolled asthma despite the use of a maximum dose of Inhaled Corticosteroids (ICS) and long acting beta 2 agonists (LABA) combination and an add-on therapy with another controller agent such as tiotropium, LTRA, or theophylline should be referred for phenotypic assessment by asthma specialists. Not only this, the use of type 2 biologics must be questioned in such patients and determined. Patients with type 2 high inflammation are eligible for type 2 biologics.

The incidence of type 2 inflammation can be seen in 50% of people diagnosed with severe asthma and responds to newer biological agents. It can be identified by increased eosinophil counts in the blood or sputum or elevated ferrous nitrous oxide inhalation. Biological therapy may be considered in patients with type 2 inflammation only if it is available and affordable. If there is no evidence of type 2 inflammation, the evaluation must be done with immunoglobulin E (IgE) testing, skin testing, sputum induction for inflammatory phenotype, bronchoscopy, and high-resolution chest computed tomography to rule out any anatomic obstruction in the respiratory system [45,46].

Medications involved in the treatment of difficult to treat asthma

Inhaled corticosteroids are the mainstay of pharmacological treatment of asthma [45]. According to a study, it is safe to add a Long-Acting Beta-2 Agonists (LABA) to inhaled corticosteroid therapy, although this does not reduce the probability of a serious exacerbation requiring hospitalization [47]. Another study identified that adding a Long-Acting Muscarinic Antagonist (LAMA) to inhaled corticosteroid therapy has superior action over adding a placebo for improving asthma control in patients 12 years or older. But, it was also identified that LAMA add-on therapy was not superior to LABA add-on therapy in terms of its efficacy [48]. The same study also revealed that the addition of a LAMA to therapy in patients already receiving a LABA plus an inhaled corticosteroid (triple therapy) does not further improve asthma control [48]. If Leukotriene Receptor Antagonists (LTRA) and a trial of a high dose of Inhaled Corticosteroid (ICS) were not already used, then it can also be added [45].

Although broad-spectrum antibiotics such as macrolides have been used as an off-label therapy for severe asthma due to their anti-inflammatory and immune-modulating effects, evidence supporting its use in difficult-to-treat asthma especially in children is still conflicting [45,49].

Biologic therapy

Therapies that target type 2 inflammation pathways include Omalizumab, Mepolizumab, Dupilumab, and Benralizumab. These subcutaneous formulations are very expensive (nearly $1,000 to 3,000 per month) and should be reserved for people with severe asthma. If Mepolizumab, Dupilumab, and Benralizumab are approved for patients of 12 years age and older, then Omalizumab is approved for patients six years and older [50]. A systematic review conducted by the Cochrane database showed that Omalizumab, being an anti-IgE monoclonal antibody, is effective in minimizing asthma exacerbations, hospitalizations, and inhaled corticosteroid dosage in patients with allergic asthma or high serum levels of IgE concentrations and is appropriate only for patients with evidence of allergic asthma on skin testing or elevated IgE [50].

Mepolizumab is also a monoclonal antibody that acts against interleukin-5 (IL-5). In some studies, it has been observed that mepolizumab, an anti-IL-5 drug not only reduces the exacerbations of severe asthma but also improve asthma-related quality of life in patients diagnosed with severe asthma and elevated eosinophil concentrations. In addition to this, Mepolizumab also reduces the need for oral corticosteroids. It is approved as an add-on maintenance therapy for patients diagnosed with severe eosinophilic asthma [51]. Benralizumab mainly targets eosinophils using the IL-5 alpha receptor. In patients with severe uncontrolled asthma, Benralizumab modestly reduces asthma exacerbations and the use of oral corticosteroids. Hence it is approved for severe eosinophilic asthmatics as an add-on maintenance therapy [52]. Dupilumab is a monoclonal antibody that targets the IL-4 alpha receptor and it has been observed that in a study of children and adolescents with moderate to severe uncontrolled asthma, those who were taking Dupilumab therapy had lower rates of severe exacerbations than those with placebo [53].

The dosage information of biologic therapy in the pediatric population is mentioned in the table 4.

Sl.no.	Name of drug	Applicable pediatric age	Recommended dose
1	Omalizumab [54].	< 6 years 6 to <12 years ≥12 years	Safety and Efficacy not established 75-375mg SC q2-4 weeks 150-375 mg SC q2-4 weeks
2	Mepolizumab [55].	< 6 years 6 to <12 years ≥12 years	Safety and Efficacy not established 40mg SC q4 weeks 100 mg SC q4 weeks
3	Dupilumab [56].	< 12 years ≥12 years	Safety and Efficacy not established 400mg SC once, then 200mg q2weeks, OR 600mg SC once, then 300mg q2weeks for patients with oral corticosteroid-dependent asthma or co-morbid moderate-to-severe atopic dermatitis (for which Dupilumab is indicated)
4	Benralizumab [57].	< 12 years ≥12 years	Safety and Efficacy not established 30mg SC q4 weeks for the first 3 doses, THEN q8weeks thereafter

Table 4: The dosage information of biologic therapy in the pediatric population.

Role of tiotropium in difficult to treat asthma

Tiotropium is a long-acting muscarinic antagonist (LAMA), which shows its action binding equally well to M1, M2 as well as M3 cholinergic receptors. After binding, it dissociates slowly from the M1 and M3 cholinergic receptors, and hence the long duration of the bronchodilator effect can be seen in patients who use tiotropium. It can be given once daily (2.5mcg), maintenance treatment of asthma in pediatric patients aged above 6 years as it has a long duration of action due to which it lasts for 35 h with maximum effect (Maximum pharmacodynamic action observed at peak concentration of drug in blood i.e. Cmax) within 60 min. Thereby by it helps in improving compliance in children [58,59].

Recently five pediatric randomized controlled trial studies regarding the use of Tiotropium in the pediatric population have shown promising results [60-65]. Tiotropium delivered via an inhaler called Respimat® Soft Mist™ inhaler has recently been approved in the USA in February 2017 for use as once-daily maintenance therapy for children with asthma over the age of 6 years old. In addition to this, Tiotropium is also recommended by GINA guidelines as an add-on therapy option at Steps 4 and 5 of asthma with a history of acute exacerbations, in patients aged 12 years and above. A study from a large clinical trial program comprising a wide spectrum of asthma severity in children and adolescents has demonstrated that Tiotropium Respimat® as an add-on therapy to inhaled corticosteroids (ICS), is not the only well-tolerated but also have efficacious bronchodilator action, resulting in improved lung function [60]. This result is also reflected in several other studies including many clinical trials which have shown improved lung function where tiotropium Respimat™ is used as an add-on therapy to ICS (Inhaled corticosteroids) in patients with poorly controlled asthma [65,66].

A study conducted by Bisgaard H and team showed that the incidences, as well as the patterns of adverse events (AE), were similar between Tiotropium Respimat® 5 mcg, 2.5 mcg, and placebo therapy, as an add-on treatment to inhaled corticosteroid with or without a secondary controlling agent, in pediatric patients aged 6-17 years experiencing symptomatic asthma [66]. Another randomized, double-blind, placebo-controlled trial study conducted by Elianne J L EVrijlandt and colleagues revealed that tolerability of Tiotropium in the pediatric population aged between 1-5 years was similar to that of a placebo, which is similar to previous findings in older populations. Although mean daytime asthma symptom scores were not significantly different between 3 groups (i.e. 2.5mcg, 5mcg, and placebo), tiotropium showed the potential to reduce the risk of asthma exacerbation in children of 1-5 years old compared with placebo [67].

Some other therapeutic approaches

A few medical regimens (nonstandard therapy) have been shown to have some clinical benefit in the treatment of refractory asthma. The use of a single dose of intramuscular triamcinolone for difficult pediatric asthmatics has been shown to reduce the inflammation and the frequency of asthma exacerbations, respectively [68]. The reasons for its effectiveness may be a combination of improved compliance, improved anti-inflammatory profile of parenteral steroids, and overcoming a relative resistance to steroids. Lastly, Immuno-modulating Agents such as the deoxyribonucleic acid (DNA) vaccine in both preclinical and early clinical stages hold promise for high therapeutic potential and may become future options for pediatric patients diagnosed with difficult-to-treat asthma [69].

Conclusion

Pediatric population with difficult-to-treat asthma is the cause of concern because despite maximal conventional treatment these patients experience frequent exacerbations of asthma. They pose a major challenge to healthcare professionals and family members because of the adverse effects of high doses of corticosteroids, impaired quality of life, continued reduction in lung function, and increased healthcare costs. The living hood of children with difficult-to-treat asthma is severely disrupted with unscheduled visits and emergency care and hospital admissions [70]. Thus management of these patients extends beyond asthma pharmacotherapy because multiple other patient-related domains need to be addressed as well. Electronic monitoring and medication adherence must be considered and measures must be taken to prevent non-compliance. The study involved a brief review on assessment of risk factors in children with difficult to treat asthma and pharmacological management that included optimal use of long-acting muscarinic antagonist (Tiotropium) and biological monoclonal antibody treatment (Omalizumab, Mepolizumab, Dupilumab, or Benralizumab) use of which is relatively new in pediatrics. Hence, individualized treatment must be preferred in these patients for optimal clinical outcomes.

Conflict of Interest

None.

Bibliography

1. Cloutier Michelle M., *et al*. "Use of asthma guidelines by primary care providers to reduce hospitalizations and emergency department visits in poor, minority, urban children". *The Journal of Pediatrics* 146.5 (2005): 591-597.

2. Williams Seymour G., *et al*. "Key clinical activities for quality asthma care. Recommendations of the National Asthma Education and Prevention Program". *MMWR Recommendations and reports: Morbidity and Mortality Weekly Report* 52.RR-6 (2003): 1-8.

3. Vos Theo., *et al*. "Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016". *The Lancet* 390.10100 (2017): 1211-1259.

4. World Health Organization. "Disease burden and mortality estimates" (2018).

5. Guilbert Theresa W., *et al*. "Severe asthma in children". *The Journal of Allergy and Clinical Immunology: In Practice* 2.5 (2014): 489-500.

6. Bousquet J., *et al*. "GINA guidelines on asthma and beyond". *Allergy* 62.2 (2007): 102-112.

7. Boulet Louis-Philippe., *et al*. "The revised 2014 GINA strategy report: opportunities for change". *Current Opinion in Pulmonary Medicine* 21.1 (2015): 1-7.

8. Sennhauser Felix H., *et al*. "The burden of asthma in children: a European perspective". *Paediatric Respiratory Reviews* 6.1 (2005): 2-7.

9. Zahran Hatice S., *et al*. "Vital signs: asthma in children—United States, 2001-2016". *Morbidity and Mortality Weekly Report* 67.5 (2018): 149.

10. Plaza-Martín A M., *et al*. "Prevalence and clinical profile of difficult-to-control severe asthma in children: Results from pneumology and allergy hospital units in Spain". *Allergologia et Immunopathologia* 42.6 (2014): 510-517.

11. Ten Brinke A., *et al*. "Risk factors of frequent exacerbations in difficult-to-treat asthma". *European Respiratory Journal* 26.5 (2005): 812-818.

12. Gendo Karna and Matthew J Lodewick. "Asthma economics: focusing on therapies that improve costly outcomes". *Current Opinion in Pulmonary Medicine* 11.1 (2005): 43-50.

13. Trivedi Michelle and Eve Denton. "Asthma in children and adults—what are the differences and what can they tell us about asthma?". *Frontiers in Pediatrics* 7 (2019): 256.

14. Bodzenta-Łukaszyk Anna., *et al*. "The statement of the Polish Society of Allergology experts on the treatment of difficult-to-treat asthma". *Advances in Respiratory Medicine* 83.4 (2015): 324-334.

15. Robinson DS., *et al*. "Systematic assessment of difficult-to-treat asthma". *European Respiratory Journal* 22.3 (2003): 478-483.

16. Le Annie V and Ronald A Simon. "The difficult-to-control asthmatic: a systematic approach". *Allergy, Asthma and Clinical Immunology* 2.3 (2006): 1-8.

17. Ullmann Nicola., *et al*. "Asthma: differential diagnosis and comorbidities". *Frontiers in Pediatrics* 6 (2018): 276.

18. Spector Sheldon. "Noncompliance with asthma therapy—are there solutions?". *Journal of asthma* 37.5 (2000): 381-388.

19. Celano Marianne, *et al*. "Treatment adherence among low-income children with asthma". *Journal of Pediatric Psychology* 23.6 (1998): 345-349.

20. Murphy A C., *et al*. "P174 Identifying non-adherence with asthma medication and the relationship to clinical outcomes amongst adults with difficult-to-control asthma". *Thorax* 65.4 (2010): A151-A151.

21. Buston Katie M and Stuart F Wood. "Non-compliance amongst adolescents with asthma: listening to what they tell us about self-management". *Family Practice* 17.2 (2000): 134-138.

22. Giraud V and N Roche. "Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability". *European Respiratory Journal* 19.2 (2002): 246-251.

23. Katon Wayne., *et al*. "The prevalence of DSM-IV anxiety and depressive disorders in youth with asthma compared with controls". *Journal of Adolescent Health* 41.5 (2007): 455-463.

24. McQuaid Elizabeth L., *et al*. "Behavioral adjustment in children with asthma: a meta-analysis". *Journal of Developmental and Behavioral Pediatrics* 22.6 (2001): 430-439.

25. Marin Teresa J., *et al*. "Double-exposure to acute stress and chronic family stress is associated with immune changes in children with asthma". *Psychosomatic Medicine* 71.4 (2009): 378.

26. Rhee Hyekyun., *et al*. "Barriers to asthma self-management in adolescents: Relationships to psychosocial factors". *Pediatric Pulmonology* 44.2 (2009): 183-191.

27. McCorkle Laura Steed. "A study of the relationships of self-efficacy of self-management of asthma and asthma self-management knowledge". Diss. Texas A&M University (2005).

28. Hauser-Cram Penny., *et al*. "I. Introduction". *Monographs of the Society for Research in Child Development* 66.3 (2001): 1-5.

29. Bauman Laurie J., *et al*. "Cumulative social disadvantage and child health". *Pediatrics* 117.4 (2006): 1321-1328.

30. Brkic Fuad., *et al*. "Cochlear implantation in children: socioeconomic family characteristics". *Medical Archives* 64.1 (2010): 25.

31. Majnemer Annette., *et al*. "Determinants of life quality in school-age children with cerebral palsy". *The Journal of Pediatrics* 151.5 (2007): 470-475.

32. Klok Ted., *et al*. "Every parent tells a story: why non-adherence may persist in children receiving guideline-based comprehensive asthma care". *Journal of Asthma* 51.1 (2014): 106-112.

33. Miller Bruce D., *et al*. "Depressed children with asthma evidence increased airway resistance:"vagal bias" as a mechanism?". *Journal of Allergy and Clinical Immunology* 124.1 (2009): 66-73.

34. Daisey Joan M., *et al*. "Indoor air quality, ventilation and health symptoms in schools: an analysis of existing information". *Indoor Air* 13.LBNL-48287 (2003).

35. Hancox R J., *et al*. "Bronchodilator tolerance and rebound bronchoconstriction during regular inhaled β-agonist treatment". *Respiratory Medicine* 94.8 (2000): 767-771.

36. Stanford Richard H., *et al*. "Short-acting β-agonist use and its ability to predict future asthma-related outcomes". *Annals of Allergy, Asthma and Immunology* 109.6 (2012): 403-407.

37. Suissa Samy., *et al*. "Low-dose inhaled corticosteroids and the prevention of death from asthma". *New England Journal of Medicine* 343.5 (2000): 332-336.

38. Ind P W., *et al*. "Anticholinergic blockade of beta-blocker-induced bronchoconstriction". *American Review of Respiratory Disease* (2012).

39. Denson-Lino J M., *et al*. "Effect of economic status on the use of house dust mite avoidance measures in asthmatic children". *Annals of Allergy* 71.2 (1993): 130-132.

40. Kim Byung-Keun., *et al*. "Evaluation and management of difficult-to-treat and severe asthma: an expert opinion from the Korean academy of asthma, allergy and clinical immunology, the working group on severe asthma". *Allergy, Asthma and Immunology Research* 12.6 (2020): 910.

41. Hew Mark., *et al*. "Systematic assessment of difficult-to-treat asthma: principles and perspectives". *The Journal of Allergy and Clinical Immunology: In Practice* 8.7 (2020): 2222-2233.

42. Giraud V and N Roche. "Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability". *European Respiratory Journal* 19.2 (2002): 246-251.

43. Fink James B and Bruce K Rubin. "Problems with inhaler use: a call for improved clinician and patient education". *Respiratory Care* 50.10 (2005): 1360-1375.

44. Dolovich M A., *et al*. "Consensus statement: aerosols and delivery devices. American Association for Respiratory Care". *Respiratory Care* 45.6 (2000): 589-596.

45. Global Initiative for Asthma - GINA. Diagnosis and Management of Difficult-to-treat and Severe Asthma - Global Initiative for Asthma – GINA (2019).

46. Narasimhan Krishnan. "Difficult-to-Treat and Severe Asthma: Management Strategies". *American Family Physician* 103.5 (2021): 286-290.

47. Busse William W., *et al*. "Combined analysis of asthma safety trials of long-acting β2-agonists". *New England Journal of Medicine* 378.26 (2018): 2497-2505.

48. Sobieraj Diana M., *et al*. "Association of inhaled corticosteroids and long-acting muscarinic antagonists with asthma control in patients with uncontrolled, persistent asthma: a systematic review and meta-analysis". *JAMA* 319.14 (2018): 1473-1484.

49. Reiter J., *et al*. "Macrolides for the long-term management of asthma-a meta-analysis of randomized clinical trials". *Allergy* 68.8 (2013): 1040-1049.

50. Normansell Rebecca., *et al*. "Omalizumab for asthma in adults and children". *Cochrane Database of Systematic Reviews* 1 (2014).

51. Ortega Hector G., *et al*. "Mepolizumab treatment in patients with severe eosinophilic asthma". *New England Journal of Medicine* 371.13 (2014): 1198-1207.

52. Nair Parameswaran., *et al*. "Oral glucocorticoid-sparing effect of benralizumab in severe asthma". *New England Journal of Medicine* 376.25 (2017): 2448-2458.

53. Castro Mario., *et al*. "Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma". *New England Journal of Medicine* 378.26 (2018): 2486-2496.

54. Wang, Kathleen Y., *et al*. "Efficacy and safety of omalizumab in pediatric patients with high immunoglobulin E levels: A case series". *Allergy and Asthma Proceedings* 39.4 (2018).

55. Licari Amelia, *et al*. "Immunomodulation in pediatric asthma". *Frontiers in Pediatrics* 7 (2019): 289.

56. Agache Ioana., *et al*. "Efficacy and safety of treatment with dupilumab for severe asthma: A systematic review of the EAACI guidelines—Recommendations on the use of biologicals in severe asthma". *Allergy* 75.5 (2020): 1058-1068.

57. Agache Ioana., *et al*. "Efficacy and safety of treatment with biologicals (benralizumab, dupilumab and omalizumab) for severe allergic asthma: A systematic review for the EAACI Guidelines-recommendations on the use of biologicals in severe asthma". *Allergy* 75.5 (2020): 1043-1057.

58. Gupta Atul., *et al*. "What is new in the management of childhood asthma?". *The Indian Journal of Pediatrics* 85.9 (2018): 773-781.

59. Vogelberg Christian. "Emerging role of long-acting anticholinergics in children with asthma". *Current Opinion in Pulmonary Medicine* 22.1 (2016): 74-79.

60. Hamelmann Eckard and Stanley J Szefler. "Efficacy and safety of tiotropium in children and adolescents". *Drugs* 78.3 (2018): 327-338.

61. Rodrigo Gustavo J and Hugo Neffen. "Efficacy and safety of tiotropium in school-age children with moderate-to-severe symptomatic asthma: A systematic review". *Pediatric Allergy and Immunology* 28.6 (2017): 573-578.

62. Hamelmann Eckard., *et al*. "Tiotropium add-on therapy in adolescents with moderate asthma: a 1-year randomized controlled trial". *Journal of Allergy and Clinical Immunology* 138.2 (2016): 441-450.

63. Hamelmann Eckard., *et al*. "A randomised controlled trial of tiotropium in adolescents with severe symptomatic asthma". *European Respiratory Journal* 49.1 (2017).

64. Vogelberg Christian, *et al*. "Tiotropium add-on therapy improves lung function in children with symptomatic moderate asthma". *The Journal of Allergy and Clinical Immunology: In Practice* 6.6 (2018): 2160-2162.

65. Szefler Stanley J., *et al*. "A phase III randomized controlled trial of tiotropium add-on therapy in children with severe symptomatic asthma". *Journal of Allergy and Clinical Immunology* 140.5 (2017): 1277-1287.

66. Bisgaard Hans., *et al*. "P154 Safety of tiotropium in pre-school children with symptomatic persistent asthma". (2016): A166-A167.

67. Vrijlandt Elianne JLE., *et al*. "Safety and efficacy of tiotropium in children aged 1-5 years with persistent asthmatic symptoms: a randomised, double-blind, placebo-controlled trial". *The Lancet Respiratory Medicine* 6.2 (2018): 127-137.

68. Panickar Jayachandran R., *et al*. "Intramuscular triamcinolone for difficult asthma". *Pediatric pulmonology* 39.5 (2005): 421-425.

69. Varga Eva-Maria., *et al*. "Immunomodulatory treatment strategies for allergic diseases". *Current Drug Targets-Inflammation and Allergy* 2.1 (2003): 31-46.

70. Velastegui Claudia, *et al*. "Impact of asthma among primary attention children". *Revista medica de Chile* 138.2 (2010): 205-212.

Volume 3 Issue 6 June 2021