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ADVANCES IN ASTHMA MANAGEMENT IN PEDIATRICS

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Abstract:
Asthma is a common condition affecting more than 300 million people around with an incidence rate of 5.3% in children. Asthma requires to be differentiated from other diseases like cystic fibrosis and bronchiectasis. As children have different bodily constitutions compared to adults, the guidelines for pharmacological therapy vary. The use of emerging therapy options eases the burden of emergency department visits. Thus, reviewing the latest advancements and therapy guidelines helps to reduce the associated morbidity and mortality.
Aim of the study: *to review the latest methodology for the management of asthma in pediatric patients*
Materials and methods: *This review is a comprehensive search of PUBMED from the year 2014 to 2024.*
Conclusion:*Asthma is a disease with a multifactorial etiology, therefore there is a need for a multi-disciplinarian approach to reduce future morbidities in pediatric patients. There is a need for the establishment of recommendations for SMART therapy in children younger than 4 years and further study into the use of biologics.*
Keywords: *asthma; management; SMART therapy; biologics*

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INTRODUCTION:

Asthma is a chronic disease characterized by airway inflammation, which leads to bronchoconstriction, edema, and mucus plugging. The disease is heterogeneous in children, with different age groups responding uniquely to various treatment modalities. Asthma is now considered an umbrella term that constitutes many endotypes and phenotypes. The majority of young patients suffering from mild to moderate asthma respond well to short-acting inhaled b2-receptor agonists (SABA), inhaled corticosteroids (ICS), and, when required, the addition of long-acting b2-agonists (LABA) and leukotriene receptor antagonists. A small percentage of young children do not respond well to traditional medicines and require a more personalized approach to management. This review will discuss various advances in the management of asthma in children. [1]

Diagnosis

Due to the complex nature of the disease, and the symptoms reported by adult studies are low on sensitivity and specificity, it is imperative to diagnose asthma as objectively as possible in children. A sizeable population of children get overdiagnosed and are treated unnecessarily with drugs that cause adverse effects. Other children may be underdiagnosed and may not receive adequate treatment to relieve their symptoms. [2]

Wheeze, shortness of breath, and cough are typically considered a triad in asthma diagnosis. Symptoms of asthma may not present at the time of clinical examination further complicating the diagnosis process. Common trigger factors such as infections, pollutants, exercise, pets, and drugs should also be identified to prevent attacks. [3]

Diagnostic Approaches

1. Phenotypes

Phenotyping is dependent on the severity of the condition, the patterns of airway inflammation, the timing and causes of symptoms, the presence or absence of atopy, and the reaction to treatments. [4]

2. Genotyping

The significance of ADAM33, a disintegrin and metalloproteinase domain 33 expressed in fibroblasts and smooth muscle cells, in controlling the lung epithelium's and fibroblasts' sensitivity to remodeling in response to allergic inflammation was brought to light by research on genes linked to asthma susceptibility. Variants in the ADAM 33 gene have been linked to a higher risk of childhood asthma. Genetic variations may potentially affect how well a patient responds to treatment. For example, the impact of polymorphisms in the gene encoding the β2-adrenergic receptor, ADRB2, on the bronchodilator response to inhaled short- and long-acting β agonists has been one of the most studied pharmacogenetic effects. [5]

3. Endotyping

Given the heterogeneous nature of asthma, the use of endotyping provides therapies that target the underlying cause of the disease with precision. Asthma can be classified based on one key immunological pathway, Type 2.[6] Type 2, T2, inflammation pathway is characterized by eosinophilic infiltration in the airway, along with overexpression of T_H2-dependent cytokines- IL-4, IL-5, and IL-6.[7]

Thus, the novel approach would be classifying patients based on T2 high asthma and T2 low asthma to provide a more customized treatment modality.[6]

a. T2- high asthma

It can be subclassified into: Early-onset atopic, Late-onset atopic, and Aspirin exacerbated respiratory disease (AERD). They have different molecular mechanisms but show resemblance in high eosinophilic count in the blood and sputum. Pediatric asthmas usually belong to the category of Early-onset T2-high asthma; beginning manifestation in childhood and into young adulthood. [6]

b. T2- low/ non- T2 asthma

This subdivision consists of Non-atopic, Smoker's asthma, Obesity-related asthma, and elderly asthma. These have variable molecular mechanisms and varying pathological pictures.[6] There is a lack of targeted therapies for T2-low asthma with a lack of response to corticosteroid therapy.[8]

Early onset T2-high asthma

It is the most common variant of asthma seen in pediatric patients. In contrast to other endotypes, this endotype is known for uncontrolled symptoms along with relatively more atopy, impaired lung function, repeated exacerbations, and steroid responsiveness. [9]

In contrast to adult patients, there is variability in the presence of inflammatory cells over time in children. These changes are irrespective of the changes in therapies targeting asthma. However, the persistence of airway eosinophilia is a peculiarity seen in a subset of children suffering from severe asthma, post-treatment with high-dose systemic corticosteroids.[4]

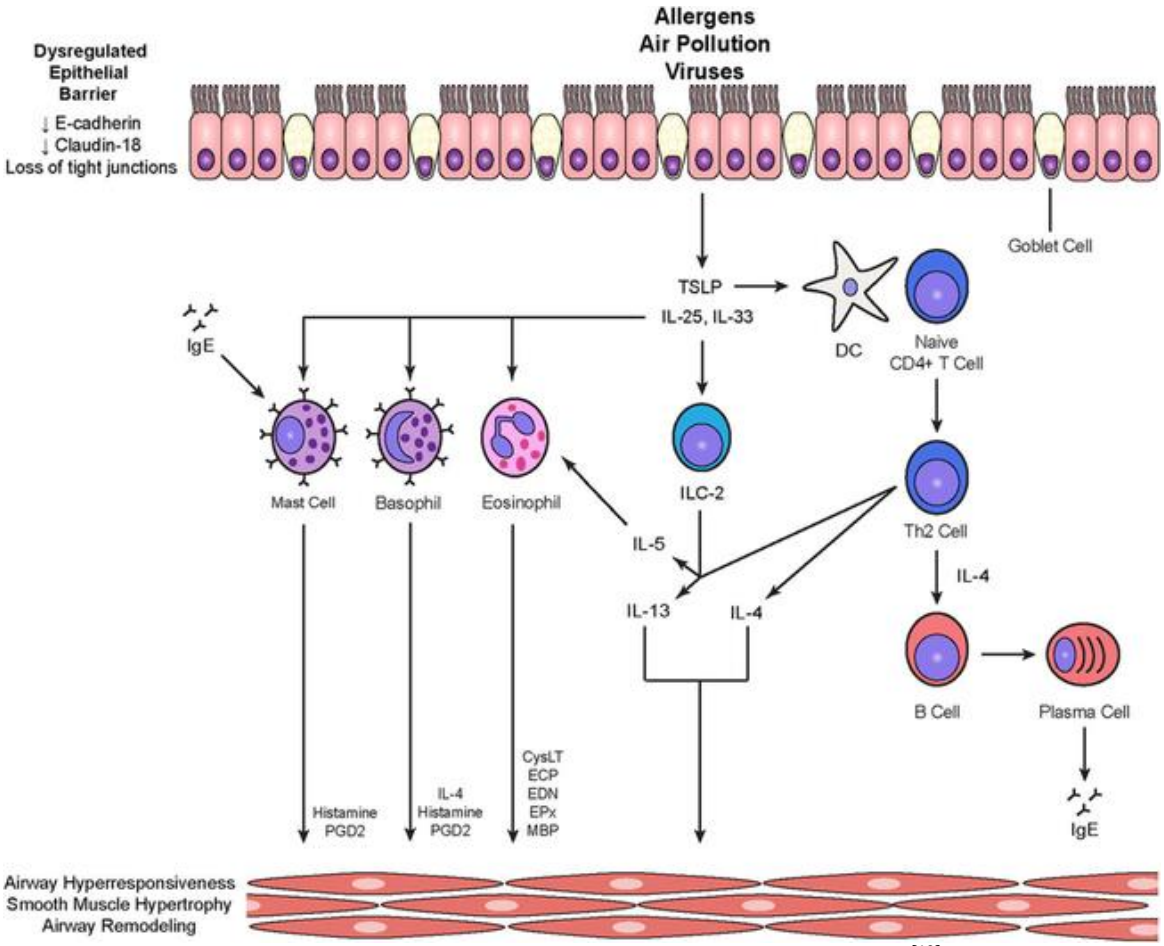

Figure 1: Type 2 Inflammatory Response in Asthma [10]

Diagnostic Methods

The establishment of diagnosis is the key to early intervention and providing specialized care to pediatric patients. As symptoms of asthma share similarities with other conditions like cystic fibrosis, primary ciliary dyskinesia, and bronchiectasis, the diagnosis must be reviewed at every clinical presentation. Overdiagnosis of the condition also risks exposing children to side effects from unnecessary treatment.[3] The Global Initiative for Asthma (GINA) states that it is imperative to test before treating, as the use of inhaled corticosteroids makes it difficult to confirm diagnosis once the asthma is under control. GINA recommends using Peak Expiratory Flow (PEF) or spirometry for diagnosis in pediatric patients under the age of 5 years. These methods are for the assessment of airway obstruction and reversibility, along with diurnal variation – which is characteristic of asthma. In older age groups, lung function tests can be used for diagnosis and monitoring the progress of treatment.[11] Other diagnostic techniques used include FeNO (for detection and quantification of airway eosinophilia) and Allergy testing (skin pricking or measurement of specific IgE levels). [3]

Other promising diagnostic techniques include the use of biomarkers and -omics approach.[12] A few potential biomarkers include vascular endothelial growth factor (VEGF) [13], sputum high mobility group box-1 (HMGB1) levels [14], sputum clusterin[15], and thymus activation-regulated chemokine (TARC) for T2-high asthma. Potential markers of severity for non-T2 pediatric asthma include increased sputum expression of IL-10 and IFN-γ, TNF-α, and thymic stromal lymphopoietin (TSLP) and interleukin (IL)-26 protein.[16] The field of RNA transcriptomics which includes blood-, sputum- and bronchial tissue transcriptomics as stated by Kuruvilla et al, provides evidence to corroborate the evidence for T2 high and T2 low asthma.[6]

Management of asthma in children

Any management of the condition should be based on the assessment criteria set by the GINA [11]:

- Assessment of control of symptoms over the past month (4 weeks)
- Identification of any risk factors affecting exacerbations, persistent limitation of airflow, or side effects
- Measurement of lung function at diagnosis/start of treatment, 3-6 months after starting ICS- ICS-containing medicine, then periodically with more frequency in cases with severe asthma

The modalities for the management of asthma encompass pharmacological, non-pharmacological, and self. Focus should also be given to the management of acute asthma attacks.

Pharmacological Modalities

It consists of maintenance therapies and reliever therapies. Maintenance therapies are the cornerstone of asthma management. The key to this modality is to avoid the usage of reliever therapies as they are indicative of poor control of asthma.[3]

MAINTENANCE THERAPIES: treatment is prescribed for use every day (or on a regularly scheduled basis)	
Inhaled Corticosteroids (ICS)	First-line maintenance agent. [11] The lowest dosage is to be given to prevent side effects and adrenal suppression.
Long-Acting Beta-2 Agonists (LABA)	Used as supplement therapy when dual ICS and Short-acting beta 2 agonists (SABA) are not effective. Increases bronchodilation duration up to 12 hours. [3]
Leukotriene receptor antagonists (Montelukast)	Used in supplementation when there is poor control despite ICS+SABA treatment [11] Adverse effects range from poor sleep to suicidal ideation [17]
Long-acting muscarinic antagonists (LAMA)	Used adjunct when there is poor symptomatic control despite ICS and LABA therapy
Oral theophylline	Used as an add-on therapy when there are uncontrolled symptoms despite several maintenance and reliever therapies Plasma levels need to be monitored on initiation of treatment and dose change

RELIEVER THERAPIES: Asthma inhaler taken as needed, for quick relief of asthma symptoms [11]	
Short-acting beta 2 agonists (SABA)	Used as first-line reliever agent The bronchodilator effect lasts for up to 4 hours
Oral corticosteroids	Used for short-term therapy to reduce inflammation of the airway and ease symptom Repeated use is suggestive of poor chronic symptomatic control and requisites review of the maintenance therapy.

SMART Therapy

Single maintenance and reliever therapy (SMART) inhalers are combined inhalers that provide both maintenance and reliever therapy. It uses one inhaler containing an ICS and immediate-acting long-acting beta-agonist (LABA). It helps to replace earlier recommended separate ICS and SABA inhalers.[17] The SMART therapy is recommended for use, per the 2020 NAEPP report and 2023 GINA report, for patients 4 or 5 years of age and older for step 3 and 4 classifications of asthma severity, respectively.[18] The therapy with its anti-inflammatory action provides symptomatic relief with bronchodilation whilst also dealing with the underlying airway inflammation. Compared to similar or higher doses of ICS or ICS/LABA therapy, SMART reduces the risk of severe exacerbations along with symptomatic control that mimics increased ICS dose at early stages of worsening asthma symptoms.[11] The benefits associated with SMART are increased adherence to therapy and earlier treatment with an ICS during exacerbations.[19]

Biologics

Biologic agents such as Omalizumab, Dupilumab, and Mepolizumab are available as subcutaneous injections or intravenous infusion and vary in frequency of use for pediatric asthma management.[20] These biologics target specific endotypes such as IgE, IL-4, and IL-5.[3][18]

Biological Agent/approved age	Route and frequency	Receptor activity/phenotype	Adverse reactions
Omalizumab/≥6 years	Subcutaneous injection every 4 weeks	Anti-IgE/ allergic asthma	Mild injection site reactions, headache, fever, abdominal pain, gastroenteritis and nasopharyngitis
Dupilumab/≥6 years	Subcutaneous injection every 2 weeks	Anti–IL-4Rα/ Moderate/severe eosinophilic/type 2 or patients requiring maintenance OCS	Mild injection site reactions and eosinophilia
Mepolizumab/≥6 years	Subcutaneous injection every 4 weeks	Anti–IL-5/5 Severe eosinophilic	Headache, attack asthma symptoms, and bronchitis

The evidence suggests that they have helped in the reduction of severe asthma exacerbations by at least 40-50% with improvements in lung function and oral corticosteroid use.[21] Omalizumab has shown promising results with its anti-IgE action for allergic asthma, with only minor adverse reactions in the form of minor injection site reactions, fever, and headache.[22][23][24] There is also ongoing research into the field of biologics that target non eosinophilic uncontrolled asthmas, such as Tezepelumab, which targets TSLP alarmin.[25] Selby et al stated that biologics are necessary add-on therapies for children with problematic severe asthma.[26] Scotney et al have reiterated the need for more clinical trials to study the efficacy of biologics in patients with severe therapy-resistant asthma.[27]

Adenotonsillectomy, bronchoscopy, and bronchoalveolar lavage

Campisi et al proposed the use of adenotonsillectomy (TA), bronchoscopy (B), and bronchoalveolar lavage (BAL) procedures for the management of severe asthma in pediatric patients. The study involved a cohort of eighteen preschool students and provided early evidence proving the feasibility of the procedure.[28]

Allergen Mitigation and Immunotherapy

Allergen-specific immunotherapy (AIT) involves the repeated administration of high-dose allergens, either subcutaneously (subcutaneous immunotherapy [SCIT]) or sublingually (sublingual immunotherapy [SLIT]), for at least 3 years to confer clinical benefits.[29] As this method involves targeting IgE antibodies, it is suggested to provide additional benefits to children with asthma.[30] Avery et al recommend the use of SCIT in adjunct to standard treatment regimes for children aged 5 years and older with mild to moderate allergic asthma.[31]

Management of Acute Asthma Attacks

AAEs or 'flare-ups' are acute or subacute episodes of progressive increases in asthma symptoms associated with airflow obstruction. They are often associated with high morbidity or even mortality. They are also the most common cause of emergency care in pediatric patients.[32]

Systemic corticosteroids such as prednisolone are the gold standard for treatment by reducing inflammation and inflammatory modulators. They help to reduce the requirement for emergency department care and hospitalization. Bronchodilators are beneficial for acute stabilization of the airway and provide time until the systemic steroid takes effect 4-8 hours later. [32] Inhaled beta-agonists such as salbutamol are often used, with the addition of ipratropium bromide for moderate/severe attacks. Aminophylline, epinephrine, and leukotriene receptor antagonists are not recommended for use. Intravenous magnesium sulfate is recommended in severe attacks with FEV1 lower than 60%.[33]

Given the urgent nature of acute asthma exacerbations (AAEs), adherence to set guidelines helps to reduce hospitalization and other complications for pediatric patients with severe AAE.[34]

CONCLUSION:

Asthma is a disease with a multifactorial etiology, therefore there is a need for a multi-disciplinarian approach to reduce future morbidities in pediatric patients. There is a need for the establishment of recommendations for SMART therapy in children

younger than 4 years and further study into the use of biologics.

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