

# **New Therapeutic Approaches in the Management and Outcomes of Pediatric Asthma**

## **Abstract**

**Background:** Asthma continues to lead to significant health issues and deaths worldwide, and there has been little progress in treatment outcomes over the past ten years, even though treatment costs have risen.

**Methodology:** This mini review compared new therapeutic approaches for treatment of pediatric asthma, searching the literature from May 2004 to August 2024 using PubMed, MEDLINE, ScienceDirect and CINAHL. Keywords such as ‘Mepolizumab,’ ‘Omalizumab,’ ‘pediatric asthma,’ and ‘biologic therapies’ were used, along with MeSH terms. After screening and full text review, 26 of 642 initial studies were selected for inclusion. This literature review explores emerging therapeutic approaches for managing pediatric asthma, focusing on monoclonal antibody treatments, inhaled corticosteroids, long-acting muscarinic antagonists (LAMAs), macrolides, vitamin D supplementation, and innovative devices like temperature-controlled laminar airflow (TLA) and electronic monitoring tools.

**Results:** In patients with severe eosinophilic asthma, monoclonal antibody therapies such as omalizumab and mepolizumab reduced exacerbations by 48% with omalizumab and 53% with mepolizumab. Long acting muscarinic antagonists and macrolides also led to improvements in lung function and a reduction in flare ups. Supplementation with vitamin D and temperature controlled laminar airflow devices were found to improve asthma control, especially in children with vitamin D deficiency and severe asthma.

**Conclusion:** Recent advancements in pediatric asthma treatment, including monoclonal antibodies, inhaled corticosteroids, non-pharmacological devices, long-acting muscarinic antagonists (LAMAs), macrolides, vitamin D supplementation have shown significant improvements in asthma control and quality of life. These therapies offer personalized approaches, particularly for children with severe asthma or specific inflammatory phenotypes. Future research should explore the long-term safety of biologics and investigate cost-effective methods to introduce these therapies in underserved regions.

**Keywords:** Pediatric asthma, biologic therapies, monoclonal antibodies, exacerbations, lung function.

## 1. Introduction

Asthma is a complex condition that involves ongoing inflammation in the airways(1). It includes symptoms like wheezing, difficulty breathing, a feeling of tightness in the chest, and coughing, which may vary over time in intensity, frequency, and occurrence(1). According to estimates from the World Health Organization, asthma impacted 262 million people and led to 455,000 deaths globally in 2019(2, 3). Given the current trends, it's anticipated that this number will hit 400 million by 2045(4). Asthma is an extremely prevalent persistent illness in children and is the main reason for them missing school, going to the Emergency Department, and being hospitalized(5). Asthma in children is one of the top 20 conditions globally when looking at disability-adjusted life years(6).

Climate change and the increase in carbon dioxide levels promote pollen growth, which is linked to higher rates of asthma in children(7). Currently, 11%–14% of children aged 5 years and older around the world report having asthma symptoms, and it's estimated that 44% of these cases are linked to environmental exposure(8). Environmental factors including dampness, air pollution, indoor mold, and tobacco smoke make asthma worse in children(9).

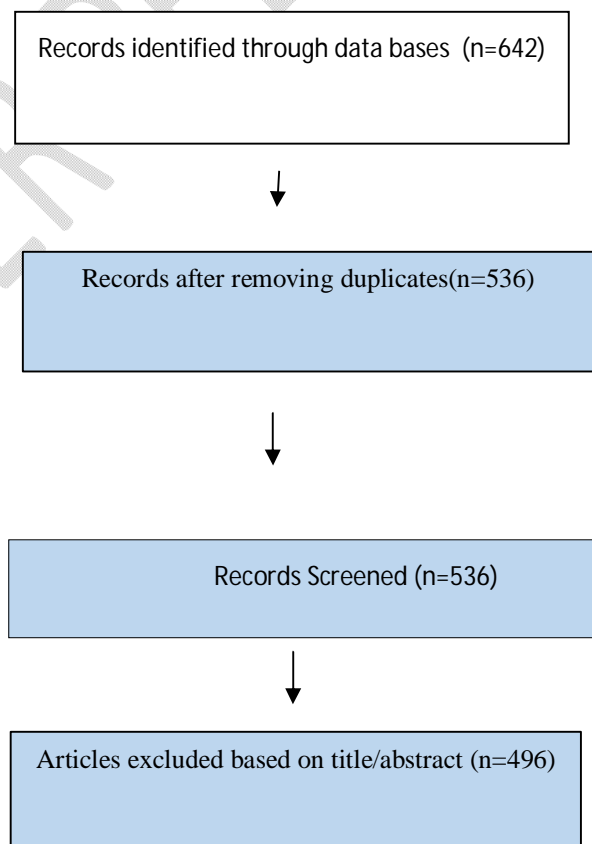
Asthma is a long-term inflammatory condition of the airways that involves increased sensitivity, both sudden and ongoing tightening of the airways, swelling, and the buildup of mucus(10). Asthma's inflammatory aspect includes various cell types, such as epithelial cells, mast cells, T lymphocytes, eosinophils, and neutrophils along with their biological products(10). Most asthma patients can achieve good long-term control with a combination of reliever therapy and controller therapy(10). Many children who have asthma usually experience mild or moderate symptoms(11). They can manage their condition well by avoiding triggers and using medications like inhaled corticosteroids short-acting inhaled b2-receptor agonists (SABA), and sometimes adding leukotriene receptor antagonists and long-acting b2-agonists when necessary(11). Even so, around 2–5% of children with asthma still experience uncontrolled symptoms, even when they are on the highest doses of standard medications, which means they need extra biological treatments(12).

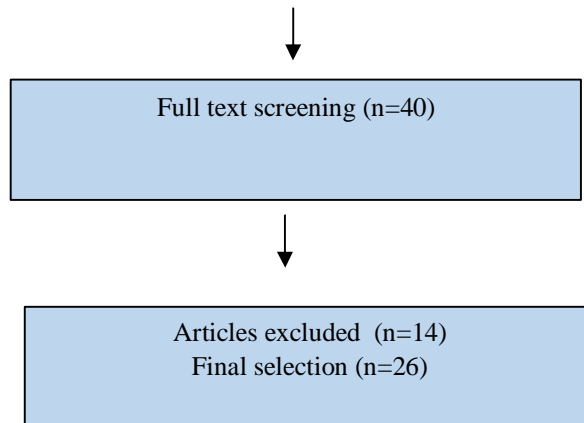
Recently, there have been a lot of new therapeutic tools for pediatric asthma, which is great for both mild and severe cases. This review aims to summarize the latest developments in asthma management and outcomes, particularly highlighting new strategies for treating pediatric asthma.

## 2. Methodology

This mini review of new therapeutic approaches in management and outcomes of pediatric asthma was performed on literature search from May 2004 to August 2024. The databases searched were PubMed, MEDLINE, ScienceDirect and CINAHL. We used the following MeSH terms and relevant keywords: ‘Mepolizumab,’ ‘Benralizumab,’ ‘Dupilumab,’ ‘Tezepelumab,’ ‘Omalizumab,’ ‘Inhaled Corticosteroids (ICS),’ ‘Tiotropium,’ ‘Macrolides (Azithromycin),’ ‘Vitamin D Supplements,’ ‘Temperature Controlled Laminar Airflow (TLA) Devices,’ ‘Electronic Monitoring Tools,’ ‘pediatric asthma,’ ‘biologic therapies,’ ‘ To retrieve relevant articles and to get precise content, we selected these MeSH terms and keywords. A total of 642 articles were retrieved from the four databases. After removing 106 duplicates, there were 536 unique records left. Of the 496 studies excluded following title and abstract screening, 496 studies were excluded as irrelevant to the research question, non-comparative design, or unsuitable outcomes. Forty studies were left for full text screening. After review of the full text articles, 14 additional studies were excluded for lack of comparative groups, improper therapeutic regimens, or adult populations. Finally, they do select 26 papers for inclusion in this review.

### Flow Chart





### 3. Literature Review Results

#### 3.1. Monoclonal Antibody Treatment

Omalizumab is the first humanized monoclonal antibody that targets IgE, and it has been studied a lot for moderate-to-severe allergic asthma(13). A study that looked at 2168 children with asthma found that omalizumab really helped reduce asthma flare-ups (risk ratio 0.52) and decreased the need for inhaled as well as oral corticosteroids, which led to better asthma control and improved quality of life(13). Real-life studies also confirmed these outcomes, showing that there were lower rates of exacerbations and less need for steroids(14, 15). In these studies, Omalizumab was mostly well tolerated, showing only mild side effects such as pain at the injection site, and there was no obvious increased risk of cancer(14, 15).

Mepolizumab, which targets IL-5, has been found to be effective in treating severe eosinophilic asthma(16). The MENSA Phase 3 study showed that there was a 53% decrease in asthma exacerbations and better lung function for adults as well as children (16). A Phase 2 study showed that in children aged 6-17 years, there was a 27% reduction in exacerbations, but there weren't any significant improvements in asthma control or lung function (17). The safety profiles observed in children matched those found in adults, and there were no new safety issues that came up. The results indicate that mepolizumab could be a useful add-on treatment for children with severe eosinophilic asthma, but we still need more information about its long-term safety and effectiveness.

Benralizumab, which targets the IL-5 receptor  $\alpha$  chain, has shown notable effectiveness in decreasing asthma exacerbations in cases of severe eosinophilic asthma(18). In Phase 3 trials, benralizumab was found to lower exacerbation rates when compared to a placebo, especially in patients who had blood eosinophil counts of 300 cells/ $\mu$ L or more(19, 20). Even though research in adolescents has shown some inconsistent findings, long-term follow-ups indicated that there are low rates of exacerbation with ongoing use in both children and adolescent groups(20). Benralizumab was mostly well tolerated, and there were no significant safety issues found in the pediatric group(20). At the same time, dupilumab, which targets IL-4 receptors, has been demonstrated to decrease severe asthma flare-ups and enhance lung function in children experiencing type 2 inflammation(21). The VOYAGE trial showed that dupilumab helped reduce exacerbations and improve asthma control in children, and it also had a good safety profile(22, 23). Lastly, tezepelumab, a drug that inhibits thymic stromal lymphopoietin (TSLP), has shown the potential to decrease asthma exacerbations and enhance asthma control in different asthma phenotypes(24). The NAVIGATOR trial showed that tezepelumab substantially decreased annual exacerbation rates in children when compared to placebo(24). The treatment was generally well accepted, with some mild side effects such as joint pain and sore throat(25). The side effects of omalizumab were mild: injection site pain, while it resulted in significant reductions in exacerbations and corticosteroid use. Both mepolizumab and benralizumab reduced exacerbations, but both require long term safety data in pediatric populations. Further study is needed to confirm safety profiles for dupilumab and Tezepelumab in children.

### **3.2. Inhaled corticosteroids**

Inhaled corticosteroids are anti-inflammatory agents used to manage persistent asthma by reducing airway inflammation. Asthma is an inflammatory condition, so it needs to be treated with anti-inflammatory agents, like inhaled corticosteroids(26). Starting treatment early with inhaled corticosteroids leads to better results, a lower chance of asthma flare-ups, and a decreased risk of death related to asthma in children (26). So, it still needs to be demonstrated if starting (or delaying) anti-inflammatory treatment changes the progression of the disease(26). It's really important to understand that using short-acting  $\beta$ 2-agonists regularly can cause tachyphylaxis, which means the receptors become tolerant quickly. This can lead to rebound bronchoconstriction, a decreased response to these medications, and even more reactions to

allergens and inflammation(27).Long term use in children may cause growth suppression by ICS. Chronic use in pediatric patients may also result in adrenal suppression(27).

### **3.3.Long-Acting Muscarinic Antagonist**

Tiotropium is a muscarinic antagonist that is widely used to manage chronic obstructive pulmonary disease(28). Acetylcholine, a neurotransmitter, is released by parasympathetic nerves in the lungs, leading to several responses, including the release of proinflammatory mediators from the airway epithelial pathways, increased mucus secretion, contraction of airway smooth muscles and enhancement of ciliary beat frequency(28). This also stimulates vasodilation and fibroblast proliferation. Tiotropium effectively binds to M1, M2, and M3 cholinergic receptors but has a slower dissociation from M1 and M3 receptors, contributing to its prolonged bronchodilatory effects(29). It is typically administered once daily, as its effects last up to 35 hours, with peak efficacy occurring within 60 minutes of administration(29).Clinical trials indicate that using tiotropium Respimat™ as an add-on therapy to inhaled corticosteroids can lead to better lung function in patients who have poorly controlled asthma(30).. Tiotropium could be a helpful and new add-on treatment choice, particularly for patients who do not achieve enough asthma control with moderate-to-high ICS, with or without the administration of LABA(30).The results from the extensive clinical trial program involving adolescents and children with varying levels of asthma severity show that tiotropium Respimat® is an effective and well-tolerated bronchodilator when used alongside inhaled corticosteroids, leading to better lung function(29).However, Tiotropium has been found to be effective in improving lung function when used with ICS, but can cause side effects including dry mouth, constipation and upper respiratory infections. Safety in pediatric populations is not well characterized, and caution should be used in the prolonged use(29).

### **3.4.Macrolides antibiotics**

Macrolides are a class of antibiotics that inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit. Macrolide antibiotics help decrease the frequency of exacerbations in bronchiectasis through their antibiotic properties or their ability to reduce inflammation(31). Brusselle et al. pointed out that macrolide antibiotics might only be beneficial for adults who have non-eosinophilic inflammation. A current investigation by Gibson and its colleagues involving 420 children with moderate or severe asthma found that oral azithromycin reduced the

occurrence of moderate flare-ups of asthma(32).While macrolides may reduce exacerbations, concerns about antibiotic resistance with long-term use must be considered. Additionally, side effects such as gastrointestinal discomfort and liver toxicity may limit their utility in pediatric patients(32).

### **3.5.Vitamin D Supplements**

Vitamin D supplements are dietary supplements that contain vitamin D, which can be in the form of vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol). There's a lot of interest in how taking vitamin D might help lower the risk of asthma flare-ups and improve control of asthma symptoms. One theory to explain how vitamin D works is that its combination of antimicrobial, antiviral, and anti-inflammatory properties might lower the exacerbation risks, which are frequently triggered by respiratory infections. Research indicates that children with asthma have been found to have insufficient vitamin D levels in different environments(33). Children with lower vitamin D levels tend to have poorer asthma control, reduced lung function, and a higher risk of exacerbations(34). Therefore, taking vitamin D can be beneficial. As a previous meta-analysis involving individuals with mostly moderate asthma indicates that vitamin D may help lower the risk of severe asthma exacerbations and reduce the need for healthcare services(35).Though Vitamin D supplementation shows promise in reducing asthma exacerbations, evidence is mixed, and further research is needed. Excessive supplementation can lead to hypercalcemia, kidney issues, and other side effects, particularly in children(35).

### **3.6.Temperature-Controlled Laminar Airflow (TLA) Devices And Electronic Monitoring Tools**

Temperature-Controlled Laminar Airflow (TLA) devices provide a sterile environment by maintaining constant airflow and temperature to protect sensitive materials from contamination. Electronic monitoring tools track parameters like temperature and humidity in real-time, ensuring TLA devices operate within specified conditions.Temperature-controlled laminar Airflow (TLA) devices and electronic monitoring tools have shown important advantages in controlling asthma(36, 37). The TLA device helps reduce allergen exposure while sleeping by providing cooled, filtered air from above. It has been shown to improve asthma-specific quality of life in patients, particularly in those with more severe asthma(36, 37). In a year-long study, people with poorly managed asthma experienced notable improvements in their symptoms and

sleep quality. At the same time, electronic monitoring devices that keep track of medication adherence and provide real-time feedback have been shown to be effective in improving asthma control(37). Research has repeatedly indicated that these devices enhance adherence rates, frequently achieving the 75-80% level needed for improved asthma management, particularly in challenging cases(37).While these tools show promise in improving asthma management, their high cost and the need for consistent use can limit accessibility in certain populations. Additionally, there may be technical issues and user compliance challenges that hinder their effectiveness(37).

Barriers to implementing emerging therapies for pediatric asthma in resource limited settings exist. They include lack of access to advanced medications, high cost of newer biologics and inadequate health care infrastructure for its administration. Healthcare providers in these areas may also be under trained in new cutting-edge treatments, making them even less accessible. Meanwhile, supply chain issues like delays on procuring medications can also force challenges. Furthermore, socioeconomic disparities and limited health literacy of patients and caregivers also impede adherence to the treatment protocols. To address these barriers, a comprehensive strategy of school-based and community educational efforts which improve healthcare access, affordability and provider education are needed.

**Table 1:Pediatric Asthma Treatment Options: Mechanisms, Efficacy, and Safety Profiles**

<b>Drug</b>	<b>Mechanism of Action</b>	<b>Pediatric Efficacy</b>	<b>Safety Profile</b>	<b>Citations</b>
<b>Omalizumab</b>	Targets IgE	Significant reduction in asthma flare-ups (RR 0.52), reduced need for corticosteroids, improved asthma control in children with moderate-to-severe asthma	Mild side effects (e.g., injection site pain), no increased cancer risk	(13, 14, 15)
<b>Mepolizumab</b>	Targets IL-5	27% reduction in exacerbations in children aged 6-17 years, though limited improvements in lung function	No new safety issues in children compared to adults	(16, 17)
<b>Benralizumab</b>	Targets IL-5	Effective in reducing	Generally well	(18, 19,

	receptor $\alpha$ chain	asthma exacerbations, especially in those with eosinophil counts >300 cells/ $\mu$ L	tolerated in pediatric populations	(20)
<b>Dupilumab</b>	Targets IL-4 receptors	Reduced severe asthma flare-ups and improved lung function in children with type 2 inflammation	Good safety profile in pediatric studies	(21, 22, 23)
<b>Tezepelumab</b>	Inhibits thymic stromal lymphopoietin (TSLP)	Reduced asthma exacerbations and improved asthma control across asthma phenotypes in children	Mild side effects (e.g., joint pain, sore throat)	(24, 25)
<b>Inhaled Corticosteroids (ICS)</b>	Anti-inflammatory	Early ICS treatment leads to fewer flare-ups and better control of asthma in children	Risk of tachyphylaxis with overuse of short-acting $\beta$ 2-agonists	(26, 27)
<b>Tiotropium</b>	Long-acting muscarinic antagonist (LAMA)	Improved lung function when used as an add-on to ICS in pediatric patients with poorly controlled asthma	Well tolerated, effective bronchodilator for adolescents	(28, 29, 30)
<b>Macrolides (e.g., Azithromycin)</b>	Antibiotic and anti-inflammatory properties	Reduction in asthma exacerbations in children with moderate-to-severe asthma	Beneficial in non-eosinophilic asthma, but further research needed	(31, 32)
<b>Vitamin D Supplements</b>	Enhances antimicrobial, antiviral, and anti-inflammatory properties	Associated with better asthma control, improved lung function, and fewer exacerbations in children with low vitamin D levels	Safe in controlled dosages	(33, 34, 35)
<b>Temperature-Controlled Laminar Airflow (TLA) Devices</b>	Reduces allergen exposure during sleep	Improved quality of life and sleep in children with poorly managed asthma	Mild side effects like discomfort reported	(36, 37)
<b>Electronic Monitoring Tools</b>	Tracks medication adherence, provides real-time feedback	Improved asthma control through enhanced medication adherence, achieving 75-80% adherence rates	No major safety concerns reported	(37)

#### 4. Conclusion

In conclusion, recent advancements in pediatric asthma management have introduced promising therapeutic approaches, including monoclonal antibodies and non-pharmacological devices, which significantly improve asthma control. Biologics targeting IgE, IL-5, IL-4/IL-13, and TSLP have shown marked reductions in asthma exacerbations and improvements in lung function and quality of life, especially for children with severe asthma or those with type 2 inflammation. Additionally, treatments like tiotropium, when used as an add-on to inhaled corticosteroids, have demonstrated effectiveness in enhancing asthma control. Non-pharmacological interventions, such as temperature-controlled laminar airflow (TLA) devices and electronic monitoring tools, have proven beneficial in reducing allergen exposure and improving adherence, key factors in managing asthma. These developments represent a significant step forward in personalized asthma care, though ongoing research is essential to optimize treatment strategies and ensure long-term safety and efficacy in diverse pediatric populations.

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