Asian Journal of Pediatric Research

Volume 14, Issue 12, Page 19-28, 2024; Article no.AJPR.125535
ISSN: 2582-2950

New Therapeutic Approaches in the Management and Outcomes of Pediatric Asthma

Thana Sarkis Karaut [a++*]

[a] Mediclinic Hospitals - L.L.C - O.P.C (Al Noor Hospital), United Arab Emirates.

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: https://doi.org/10.9734/ajpr/2024/v14i12406

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/125535

Minireview Article

Received: 14/09/2024
Accepted: 16/11/2024
Published: 22/11/2024

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.

[++] Specialist Pediatrics;
**Corresponding author: Email: drthanasarkiskaraut@gmail.com;*

Cite as: *Karaut, Thana Sarkis. 2024. "New Therapeutic Approaches in the Management and Outcomes of Pediatric Asthma". Asian Journal of Pediatric Research 14 (12):19-28. https://doi.org/10.9734/ajpr/2024/v14i12406.*

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 (Reddel et al. 2022). 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 (Reddel et al. 2022). According to estimates from the World Health Organization, asthma impacted 262 million people and led to 455,000 deaths globally in 2019 (Global Burden of Disease Study 2020, World Health Organization 2024). Given the current trends, it's anticipated that this number will hit 400 million by 2045 (Masoli et al. 2004). 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 (Roh 2024). Asthma in children is one of the top 20 conditions globally when looking at disability-adjusted life years (Serebrisky and Wiznia 2019).

Climate change and the increase in carbon dioxide levels promote pollen growth, which is linked to higher rates of asthma in children (Channar et al. 2023). 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 (Latorre et al. 2022). Environmental factors including dampness, air pollution, indoor mold, and tobacco smoke make asthma worse in children (Mamluk et al. 2024).

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 (GIFA 2010). Asthma's inflammatory aspect includes various cell types, such as epithelial cells, mast cells, T lymphocytes, eosinophils, and neutrophils along with their biological products (GIFA 2010). Most asthma patients can achieve good long-term control with a combination of reliever therapy and controller therapy (GIFA 2010). Many children who have asthma usually experience mild or moderate symptoms (Porsbjerg et al. 2023). 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 (Porsbjerg et al. 2023). 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 (Andrenacci et al. 2022).

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.

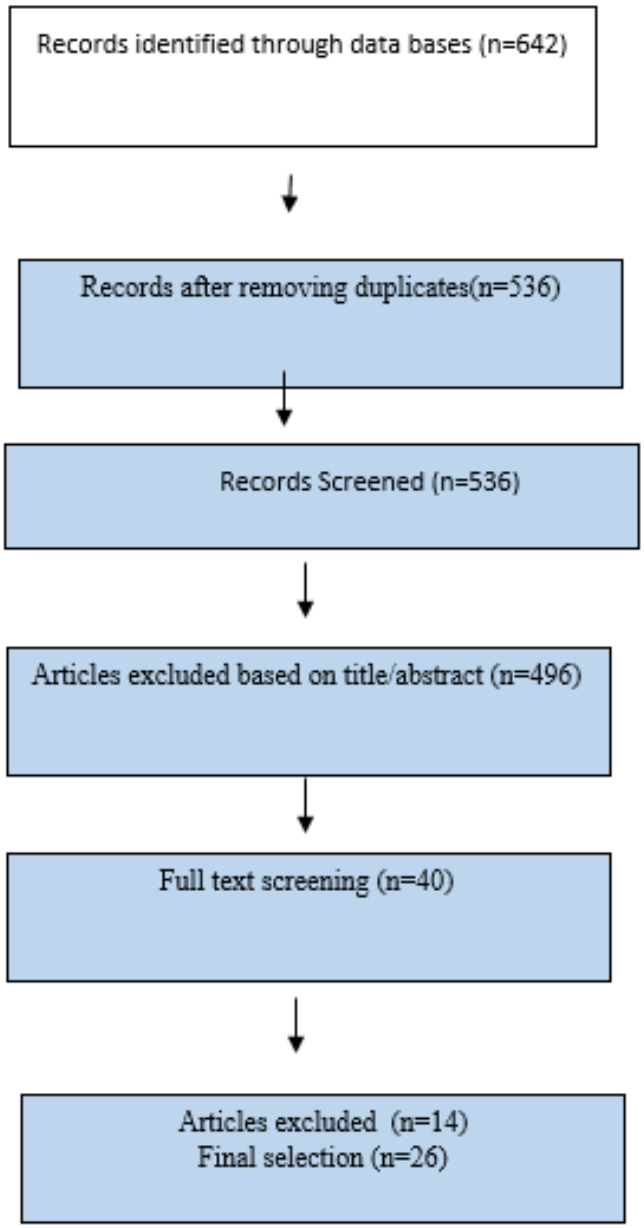

Fig. 1. Flow chart

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 (Liu et al. 2022). 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 (Liu et al. 2022). Real-life studies also confirmed these outcomes, showing that there were lower rates of exacerbations and less need for steroids (Pitrez et al. 2017, Deschildre et al. 2013). 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 (Pitrez et al. 2017, Deschildre et al. 2013).

Mepolizumab, which targets IL-5, has been found to be effective in treating severe eosinophilic asthma (Ortega et al. 2014). 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 (Ortega et al. 2014). 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 (Jackson et al. 2022). 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 α chain, has shown notable effectiveness in decreasing asthma exacerbations in cases of severe eosinophilic asthma (Bleecker et al. 2016). 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/μL or more (FitzGerald et al. 2016, Busse et al. 2021). 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 (Busse et al. 2021). Benralizumab was mostly well tolerated, and there were no significant safety issues found in the pediatric group (Busse et al. 2021). 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 (Bacharier et al. 2021). The VOYAGE trial showed that dupilumab helped reduce exacerbations and improve asthma control in children, and it also had a good safety profile (Jackson et al. 2023, Castro et al. 2018). 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 (Menzies-Gow et al. 2023). The NAVIGATOR trial showed that tezepelumab substantially decreased annual exacerbation rates in children when compared to placebo (Menzies-Gow et al. 2023). The treatment was generally well accepted, with some mild side effects such as joint pain and sore throat (Brusselle and Koppelman 2022). 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 (Papi et al. 2018). 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 (Papi et al. 2018). So, it still needs to be demonstrated if starting (or delaying) anti-inflammatory treatment changes the progression of the disease (Papi et al. 2018). It's really important to understand that using short-acting β2-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 (Abrams et al. 2016). Long term use in children may cause growth suppression by ICS. Chronic use in pediatric patients may also result in adrenal suppression (Abrams et al. 2016).

3.3 Long-Acting Muscarinic Antagonist

Tiotropium is a muscarinic antagonist that is widely used to manage chronic obstructive pulmonary disease (Vogelberg 2016). 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 (Vogelberg 2016). 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 (Hamelmann and Szefler 2018). It is typically administered once daily, as its effects last up to 35 hours, with peak efficacy occurring within 60 minutes of administration (Hamelmann and Szefler 2018). 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 (Bush and Griffiths 2017). 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 (Bush and Griffiths 2017).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 (Hamelmann and Szefler 2018). 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 (Hamelmann and Szefler 2018).

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 (Brusselle et al. 2013). Brusselle et al. (2013) 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 (Gibson et al. 2017). 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 (Gibson et al. 2017).

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 (Gupta et al. 2012). Children with lower vitamin D levels tend to have poorer asthma control, reduced lung function, and a higher risk of exacerbations (Gupta et al. 2011). 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 (Martineau et al. 2016). 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 (Martineau et al. 2016).

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

Table 1. Pediatric asthma treatment options: mechanisms, efficacy, and safety profiles

Drug	Mechanism of Action	Pediatric Efficacy	Safety Profile	Citations
Omalizumab	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	(Liu et al. 2022, Pitrez et al. 2017, Deschildre et al. 2013)
Mepolizumab	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	(Ortega et al. 2014, Ortega et al. 2022)
Benralizumab	Targets IL-5 receptor α chain	Effective in reducing asthma exacerbations, especially in those with eosinophil counts >300 cells/μL	Generally well tolerated in pediatric populations	(Bleecker et al. 2016, Bleecker et al. 2016, Busse et al. 2021)
Dupilumab	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	(Bacharier et al. 2021, Jackson et al. 2023, Castro et al. 2018)
Tezepelumab	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)	(Menzies-Gow et al. 2021, Brusselle and Koppelman et al. 2022)
Inhaled Corticosteroids (ICS)	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 β2-agonists	(Papi et al. 2018, Abrams et al. 2016)
Tiotropium	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	(Vogelberg 2016, Hamelmann and Szefler 2018, Bush and Griffiths 2017)
Macrolides (e.g., Azithromycin)	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	(Brusselle et al. 2013, Gibson et al. 2017)
Vitamin D Supplements	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	(Gupta et al. 2012, Gupta, et al. 2011, Martineau et al. 2016)
Temperature-Controlled Laminar Airflow (TLA) Devices	Reduces allergen exposure during sleep	Improved quality of life and sleep in children with poorly managed asthma	Mild side effects like discomfort reported	(Warner, 2017, Boyle et al. 2017)
Electronic Monitoring Tools	Tracks medication adherence, provides real-time feedback	Improved asthma control through enhanced medication adherence, achieving 75-80% adherence rates	No major safety concerns reported	(Boyle et al. 2012)

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 (Warner 2017, Boyle et al. 2012). 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 (Warner 2017, Boyle et al. 2012). 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 (Boyle et al. 2012). 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 (Boyle et al. 2012). 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 (Boyle et al. 2012).

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.

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.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

Abrams, E. M., Szefler, S. J., & Becker, A. B. (2016). Effect of asthma therapies on the natural course of asthma. *Journal of Asthma and Immunology, 117*(6), 627–633. https://doi.org/10.1016/j.anai.2016.09.438

Andrenacci, B., Ferrante, G., Roberto, G., Piacentini, G., La Grutta, S., Marseglia, G. L., et al. (2022). Challenges in uncontrolled asthma in pediatrics: Important considerations for the clinician. *European Journal of Pediatric Allergy and Immunology*, *18*(8), 807–821. https://doi.org/10.1080/1744666X.2022.2093187

Bacharier, L. B., Maspero, J. F., Katelaris, C. H., Fiocchi, A. G., Gagnon, R., de Mir, I., et al. (2021). Dupilumab in children with uncontrolled moderate-to-severe asthma. *New England Journal of Medicine*, *385*(24), 2230–2240. https://doi.org/10.1056/NEJMoa2106567

Bleecker, E. R., FitzGerald, J. M., Chanez, P., Papi, A., Weinstein, S. F., Barker, P., et al. (2016). Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): A randomised, multicentre, placebo-controlled phase 3 trial. *Lancet (London, England)*, *388*(10056), 2115–2127. https://doi.org/10.1016/S0140-6736(16)31324-1

Boyle, R. J., Pedroletti, C., Wickman, M., Bjermer, L., Valovirta, E., Dahl, R., et al. (2012). Nocturnal temperature-controlled laminar airflow for treating atopic asthma: A randomised controlled trial. *Thorax, 67*(3), 215–221. https://doi.org/10.1136/thoraxjnl-2011-200665

Brusselle, G. G., & Koppelman, G. H. (2022). Biologic therapies for severe asthma. *New England Journal of Medicine, 386*(2), 157–171.

Brusselle, G. G., VanderStichele, C., Jordens, P., Deman, R., Slabbynck, H., Ringoet, V., et al. (2013). Azithromycin for prevention of exacerbations in severe asthma (AZISAST): A multicentre randomised double-blind placebo-controlled trial. *Thorax, 68*(4), 322–329. https://doi.org/10.1136/thoraxjnl-2012-202698

Bush, A., & Griffiths, C. J. (2017). Improving treatment of asthma attacks in children. *British Medical Journal Publishing Group*. https://doi.org/10.1136/bmj.j5763

Busse, W. W., Bleecker, E. R., FitzGerald, J. M., Ferguson, G. T., Barker, P., Brooks, L., et al. (2021). Benralizumab for adolescent patients with severe, eosinophilic asthma: Safety and efficacy after 3 years of treatment. *Journal of Allergy and Clinical Immunology*, *148*(1), 266–271.e2. https://doi.org/10.1016/j.jaci.2021.02.009

Castro, M., Corren, J., Pavord, I. D., Maspero, J., Wenzel, S., Rabe, K. F., et al. (2018). Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *New England Journal of Medicine, 378*(26), 2486–2496. https://doi.org/10.1056/NEJMoa1804092

Channar, N., Dayo, A., Ghoto, M. A., Shah, S. M., & Zaman, K. JLMRJ. (2023). Evaluation of asthma: Aggravating factors and family history—a prospective observational study. *Journal of Lung, Multidisciplinary Respiratory Journal*, *5*(2).

Deschildre, A., Marguet, C., Salleron, J., Pin, I., Rittié, J.-L., Derelle, J., et al. (2013). Add-on omalizumab in children with severe allergic asthma: A 1-year real-life survey. *European Respiratory Journal*, *42*(5), 1224–1233. https://doi.org/10.1183/09031936.00149812

FitzGerald, J. M., Bleecker, E. R., Nair, P., Korn, S., Ohta, K., Lommatzsch, M., et al. (2016). Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): A randomised, double-blind, placebo-controlled phase 3 trial. *Lancet (London, England)*, *388*(10056), 2128–2141. https://doi.org/10.1016/S0140-6736(16)31322-8

Gibson, P. G., Yang, I. A., Upham, J. W., Reynolds, P. N., Hodge, S., James, A. L., et al. (2017). Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): A randomised, double-blind, placebo-controlled trial. *Lancet, 390*(10095), 659–668.

Global Burden of Disease Study 2019. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet (London, England)*, *396*(10258), 1204–1222. https://doi.org/10.1016/S0140-6736(20)32226-1

Global Initiative for Asthma (GIFA). (2022). Global strategy for asthma management and prevention.

Gupta, A., Bush, A., Hawrylowicz, C., & Saglani, S. (2012). Vitamin D and asthma in children. *Paediatric Respiratory Reviews, 13*(4), 236–243. https://doi.org/10.1016/j.prrv.2011.07.003

Gupta, A., Sjoukes, A., Richards, D., Banya, W., Hawrylowicz, C., Bush, A., et al. (2011). Relationship between serum vitamin D, disease severity, and airway remodeling in children with asthma. *American Journal of Respiratory and Critical Care Medicine, 184*(12), 1342–1349.

https://doi.org/10.1164/rccm.201107-1239OC

Hamelmann, E., & Szefler, S. J. (2018). Efficacy and safety of tiotropium in children and adolescents. *Journal of Drug Therapy, 78*(3), 327–338. https://doi.org/10.1007/s40265-018-0862-1

Jackson, D. J., Bacharier, L. B., Gergen, P. J., Gagalis, L., Calatroni, A., Wellford, S., et al. (2022). Mepolizumab for urban children with exacerbation-prone eosinophilic asthma in the USA (MUPPITS-2): A randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet (London, England)*, *400*(10351), 502–511. https://doi.org/10.1016/S0140-6736(22)01198-9

Jackson, D. J., Bacharier, L. B., Phipatanakul, W., Sher, L., Domingo, C., Papadopoulos, N., et al. (2023). Dupilumab pharmacokinetics and effect on type 2 biomarkers in children with moderate-to-severe asthma. *Annals of Allergy, Asthma & Immunology*, *131*(1), 44–51.e4. https://doi.org/10.1016/j.anai.2023.03.014

Latorre, C. C., Colon, S. M., Diaz, A. D. R., Ferrer, V. F., Perez, M. M., Hernandez, I. L., et al. (2022). Environmental and occupational factors: Contribution and perspectives on difficult-to-treat asthma. In *New Perspectives on Asthma* (pp. 1-18). IntechOpen. https://doi.org/10.5772/intechopen.108605

Liu, L., Zhou, P., Wang, Z., Zhai, S., & Zhou, W. J. F. I. P. (2022). Efficacy and safety of omalizumab for the treatment of severe or poorly controlled allergic diseases in children: A systematic review and meta-analysis. *Frontiers in Pediatrics*, *10*, 851177. https://doi.org/10.3389/fped.2022.851177

Mamluk, M. S., & Karadakhy, K. A. J. A. (2024). Aggravating factors of asthma among patients visited respiratory center at Shar Hospital outpatient in Sulaymaniyah-Kurdistan-Iraq. *Journal of Asthma*, *9*(2), 19–26.

Martineau, A. R., Cates, C. J., Urashima, M., Jensen, M., Griffiths, A. P., Nurmatov, U., et al. (2016). Vitamin D for the management of asthma. *Cochrane Database of Systematic Reviews, 9*. https://doi.org/10.1002/14651858.CD011511.pub3

Masoli, M., Fabian, D., Holt, S., Beasley, R., & Program GIfA. (2004). The global burden of asthma: Executive summary of the GINA Dissemination Committee Report. *European Respiratory Journal*, *59*(5), 469–478. https://doi.org/10.1111/j.1398-9995.2004.00526.x

Menzies-Gow, A., Corren, J., Bourdin, A., Chupp, G., Israel, E., Wechsler, M. E., et al. (2021). Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *New England Journal of Medicine, 384*(19), 1800–1809. https://doi.org/10.1056/NEJMoa2034975

Ortega, H. G., Liu, M. C., Pavord, I. D., Brusselle, G. G., FitzGerald, J. M., Chetta, A., et al. (2014). Mepolizumab treatment in patients with severe eosinophilic asthma. *New England Journal of Medicine*, *371*(13), 1198–1207. https://doi.org/10.1056/NEJMoa1403290

Papi, A., Brightling, C., Pedersen, S. E., & Reddel, H. K. (2018). Asthma. *Lancet, 391*(10122), 783–800.

Pitrez, P. M., de Souza, R. G., Roncada, C., Heinzmann-Filho, J. P., Santos, G., Pinto, L. A., et al. (2017). Impact of omalizumab in children from a middle-income country with severe therapy-resistant asthma: A real-life study. *Pediatric Pulmonology*, *52*(11), 1408–1413. https://doi.org/10.1002/ppul.23845

Porsbjerg, C., Melén, E., Lehtimäki, L., & Shaw, D. (2023). Asthma. *Lancet (London, England)*, *401*(10379), 858–873.

Reddel, H. K., Bacharier, L. B., Bateman, E. D., Brightling, C. E., Brusselle, G. G., Buhl, R., et al. (2022). Global Initiative for Asthma Strategy 2021: Executive Summary and Rationale for Key Changes. *American Journal of Respiratory and Critical Care Medicine*, *205*(1), 17–35. https://doi.org/10.1016/j.jaip.2021.10.001

Roh, E. J. (2024). Comparison and review of international guidelines for treating asthma in children. *Clinical and Experimental Pediatrics*, *67*(9), 447–455. https://doi.org/10.3345/cep.2022.01466

Serebrisky, D., & Wiznia, A. (2019). Pediatric asthma: A global epidemic. *Annals of Global Health*, *85*(1). https://doi.org/10.5334/aogh.2416

Vogelberg, C. J. (2016). Emerging role of long-acting anticholinergics in children with asthma. *Current Opinion in Pediatric Medicine, 22*(1), 74–79. https://doi.org/10.1097/MCP.0000000000000229

Warner, J. O. (2017). Use of temperature-controlled laminar airflow in the management of atopic asthma: Clinical evidence and experience. *Journal of Allergy and Respiratory Diseases, 11*(4), 181–188. https://doi.org/10.1177/1753465817690505

World Health Organization. (2024). Asthma [Internet]. Geneva (Switzerland). Available from: https://www.who.int/news-room/factsheets/detail/asthma

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/125535