Review Article

Vayu: Ventilation Advances Yielding Uplift in Asthma Care

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ABSTRACT

Asthma, a prevalent and complex respiratory disease affecting over 300 million people worldwide, requires personalized treatment approaches due to its diverse clinical presentations and underlying mechanisms. Traditional therapies, like glucocorticoids, are often ineffective for severe cases, leading to the development of biologics targeting specific inflammatory pathways, such as anti-IgE, anti-IL-5, and anti-IL-4/IL-13 treatments. These biologics provide promising solutions for patients with difficult-to-control asthma, improving disease management and reducing reliance on corticosteroids. In addition to these pharmacologic advancements, technology plays a key role in transforming asthma care. Artificial intelligence (AI) is enhancing diagnostic processes and predicting asthma exacerbations, while digital smart inhalers (DSIs) improve medication adherence by monitoring inhaler usage and providing real-time feedback to patients and healthcare providers. Telemedicine, including virtual consultations and remote patient monitoring, enhances accessibility and care coordination, especially for underserved populations. However, infrastructure limitations and digital literacy remain, requiring further innovation and research. Overall, the future of asthma care hinges on the integration of biologics, AI, and telemedicine to offer more effective, patient-centered care, ultimately improving outcomes and minimizing the burden of this chronic disease.

Keywords: Asthma, Biologics, Artificial intelligence (AI), Telemedicine, Digital smart inhalers (DSIs).

1. INTRODUCTION

Asthma is a major respiratory disease that affects around 300 million individuals globally. Clinically, it is identified by a classic constellation of symptoms (cough, wheeze, shortness of breath, and chest tightness) and signs of expiratory airflow restriction. Symptoms and airflow restriction might vary greatly across individuals and within one patient at different points in time.[1] It is significantly more common in women (10.4%) than in men (6.2%), and among people living in poverty (11.8).[2] Asthma diagnosis requires consideration of both classical and atypical symptoms. While intermittent dyspnea, wheezing, and cough are typical, asthma may also present with less specific symptoms such as isolated cough. Therefore, asthma should be considered even in the absence of classical symptoms, with a concurrent evaluation for alternative diagnoses. The diagnosis is primarily clinical but can be supported by objective measurements like reversible airflow obstruction. Guidelines emphasize a detailed history, including identifying common triggers, work exposures, exercise-induced symptoms, and family history of asthma [3]. Diagnostic testing for patients over five years old includes spirometry with bronchodilator response and bronchoprovocation testing when airflow obstruction is not evident. Additional tests, such as exhaled fractional nitric oxide, CBC with differential to assess eosinophilia, serum IgE levels, and allergy testing, are recommended for persistent or severe cases, along with imaging (chest X-ray or CT scan) and alpha-1 antitrypsin levels. Alternate diagnoses should be considered in cases of persistent or severe asthma, including COPD, bronchiectasis, sarcoidosis, or obstructions due to masses or foreign objects. Dyspnea may also indicate cardiovascular disease, obesity, anemia, or interstitial lung disease. Chronic cough, even without other asthma symptoms, requires evaluation for infections, acid reflux, aspiration, or interstitial lung disease.[4] For children, considerations include cystic fibrosis, immunodeficiency, and foreign body aspiration. Advanced diagnostic procedures, such as bronchoscopy with BAL, endobronchial biopsies, or ultrasound-guided lymph node biopsies, may be necessary in severe cases to confirm asthma or exclude alternative diagnoses.

Pathogenesis of asthma is a very complex and multifactorial process involving several genetics to environmental factors. It is believed that four main pivotal factors playing a major role in pathogenesis are Th2-high inflammation, Th2-low inflammation, airway hyperresponsiveness, and airway remodeling.[5] Patients with asthma differ significantly in terms of clinical features, disease severity, degree and pattern of underlying airway inflammation, airway hyperresponsiveness (AHR), and airway remodeling.[6]

Asthma is a heterogeneous condition characterized by diverse phenotypes and endotypes, which help distinguish patient subgroups and support personalized care. Phenotypes are shared clinical features that vary among patients. Childhood-onset asthma is associated with elevated IgE levels, low lung function, and greater airway hyperresponsiveness, while adult-onset asthma tends to be more severe, less linked to allergies, and more influenced by environmental factors. Genetic studies reveal that childhood-onset asthma involves a higher genetic risk, particularly at the 17q12-23 locus, whereas adult-onset asthma shares some genetic risk, notably in the HLA region

on chromosome 6.[7,8] Severe asthma clusters identified by the Severe Asthma Research Program (SARP) highlight differences based on age of onset, allergen sensitization, lung function, and comorbidities, with frequent exacerbators displaying higher blood eosinophil counts, BMI, and bronchodilator responsiveness. [9] Other studies, such as U-BIOPRED and the Severe and Uncontrolled Asthma Registry (Italy), have further contributed to understanding severe asthma phenotypes, with frequent exacerbators showing elevated fractional nitric oxide excretion and a history of smoking. [10]

Asthma endotypes focus on underlying mechanisms, often characterized by immune and molecular pathways. Th2 inflammation plays a prominent role in severe asthma, with biomarkers like IgE, blood eosinophil counts, and soluble ST2 (IL-33 receptor) linked to exacerbations.[11] Genetic studies have identified over 60 loci associated with asthma severity, including IL33, IL1RL1, and CDHR3, as well as gene expression patterns varying across tissues like airway epithelium and blood .[12] Proteomic analyses show distinct sputum protein profiles among subgroups, such as smokers, while metabolomic studies reveal immune-related differences, although corticosteroid use complicates interpretations. [13] The airway microbiome also influences severe asthma, with specific bacteria like Pseudomonadaceae and Enterobacteriaceae linked to phenotypes and Actinobacteria correlating with corticosteroid responsiveness. [14] Together, these findings emphasize the complexity of asthma and the need to integrate clinical and molecular insights for effective management.

2. CURRENT TREATMENT ADVANCES:

Glucocorticoids have been the first-line therapy for asthma for many years. Despite being the standard asthma treatment, Glucocorticoids have two major disadvantages, first, they can have dangerous side effects that are highly dose-dependent, and second, they can cause refractory responses in asthma patients, especially those with severe asthma. A decrease of less than 15% in forced expiratory volume in one second (FEV1) following two weeks of adequate dosage steroid therapy is considered steroid resistance. However, β2-adrenergic agonist-mediated vasodilation does work effectively for these individuals. Most asthma patients find that inhaled corticosteroids improve lung function and reduce exacerbations. To treat their severe asthma, patients need higher dosages of oral glucocorticoids, and 5–10% of these individuals do not react well to these medications, which leads to difficult-to-manage asthma symptoms and the diagnosis of steroid-resistant asthma. Th2-low asthma phenotypes are more likely to develop severe asthma and react less well to steroid treatment. However, individuals with chronic eosinophil inflammation have been seen to have glucocorticoid insensitivity.

New biologics that target various inflammatory pathways are developed in light of recent findings in the pathophysiology of asthma. These include treatments that target IL-33 and epithelial-derived thymic stromal lymphopoietin (TSLP), anti-IL-5, anti-IL4/13, and several treatments that target the Th2-low. [15]

2.2 BIOLOGICS

2.2.1 Anti IgE:

The first biologic to be licensed for the treatment of asthma in the United States and in the European Union was omalizumab, a humanized anti-IgE monoclonal antibody. By blocking its binding to the FcεRI receptor on mast cells and basophils, it inhibits IgE, a crucial component of the inflammatory cascade of allergic asthma, hence lowering the release of proinflammatory mediators and allergic reactions. Omalizumab further reduces inflammation by downregulating the expression of FcεRI. Furthermore, research indicates that omalizumab increases the production of IFN-α during viral infections, suggesting possible antiviral pathways. [16]

With modest improvements in lung function, especially in severe allergic asthma, clinical trials and real-world research have shown its effectiveness in lowering hospitalizations, corticosteroid use, and asthma exacerbations. There was a 25% decrease in exacerbations and other positive results, according to a Cochrane review of 25 randomized controlled studies. However, there is still conflicting evidence about the reduction of oral corticosteroid usage. Omalizumab has demonstrated efficacy in patients with both T2-high and T2-low asthma profiles, as well as in those with IgE levels outside the authorized range.[17] However, retrospective analyses suggest that patients with high eosinophil counts and elevated fractional exhaled nitric oxide (FeNO) levels may benefit more.

With age-specific IgE level restrictions, omalizumab is authorized for use in children and adults with moderate to severe allergic asthma that is not well managed with inhaled corticosteroids. Its dosage is determined by body weight and pretreatment IgE levels and is administered subcutaneously every two to four weeks. To determine efficacy, a three to six-month trial period is advised; if successful, therapy can go on permanently. Although the medication is usually well accepted, there is a 0.1–0.2% chance of anaphylaxis, hence it must be administered in medical facilities that are prepared for such situations. Because of this danger, the FDA requires monitoring periods after injections. [18]

2.2.2 Anti–IL-5:

Mepolizumab, reslizumab, and bevacizumab are examples of anti-IL-5 medications that target eosinophilic asthma, which is characterized by elevated eosinophil counts and recurrent flare-ups even after corticosteroid therapy. Anti-IL-5 biologics decrease eosinophilic airway inflammation by blocking IL-5 or its receptor, which is essential for eosinophil recruitment and survival. Benralizumab uses antibody-directed cell-mediated cytotoxicity to specifically cause eosinophil apoptosis. [19]

Mepolizumab has shown promise in lowering exacerbations, controlling asthma, and decreasing the need for oral corticosteroids, while there has been considerable variation in the benefits of lung function. A 50% decrease in exacerbations and small improvements in lung function have been seen in clinical studies, such as SIRIUS and DREAM. [20,21] When given intravenously, reslizumab efficiently lowers exacerbations and enhances lung function, especially in patients with AEC ≥400 cells/µl; however, its effects on oral corticosteroid-sparing are yet unknown.[22] Benralizumab also lowers the usage of oral corticosteroids and exacerbations; the advantages are greatest for those with AEC ≥300 cells/µl.

In the ZONDA trial, it reduced oral corticosteroid use by 75% and annual exacerbations by 70%. [23,24]

These therapies are approved for patients with severe eosinophilic asthma, with specific dosing and administration protocols. Reslizumab needs to be infused intravenously, whereas mepolizumab and benralizumab are administered subcutaneously. Although all pose the potential of hypersensitivity events, including anaphylaxis, safety profiles are typically positive. Research emphasizes the necessity of tailored strategies since systemic indicators and local eosinophilic inflammation cannot always coincide, and certain individuals might need greater dosages or intravenous formulations. [25] To help choose the best course of therapy, head-to-head comparisons of different treatments are required.

2.2.3 Anti–IL-4/IL-13:

The cytokines IL-4 and IL-13, which are essential for the synthesis of IgE, the recruitment of inflammatory cells, goblet cell hyperplasia, airway remodeling, and hyperresponsiveness, are blocked by dupilumab, a monoclonal antibody that targets the IL-4α receptor. Targeting IL-4 or IL-13 separately has disadvantages, which our combined blockage overcomes. [26] Dupilumab is effective in improving lung function, lowering asthma flare-ups, and reducing the usage of oral corticosteroids by as much as 70%. Almost half of patients who were reliant on these medications were able to stop using them. These advantages are more noticeable in individuals with elevated baseline levels of blood eosinophils and FeNO, and they coincide with decreases in T2 inflammatory indicators including FeNO and IgE.

Furthermore, dupilumab has demonstrated advantages in individuals with nasal polyposis and chronic rhinosinusitis, which makes it a recommended choice in these situations. In contrast to anti-IL-5 treatments, FeNO levels indicate how well a patient will respond to dupilumab. This is probably because it regulates inducible nitric oxide synthase and mucus formation via STAT-6 pathways. Although injection site reactions and temporary eosinophilia are typical adverse effects, its safety profile is excellent. As a flexible therapy for T2 inflammation-driven disorders, dupilumab has FDA approval for both atopic dermatitis and asthma. [27]

3. CURRENT TECHNOLOGICAL ADVANCES IN ASTHMA CARE:

3.1 artificial intelligence (AI) in asthma care:

The use of artificial intelligence (AI) in asthma treatment is growing in importance as it provides improvements in patient management, diagnosis, and monitoring. An AI system integrated with a sensor was utilized to assess ambient radio reflections in the field of medication self-administration (MSA), which is one prominent application. This novel method achieved a remarkable Area Under the Curve (AUC) of 0.992 in recognizing correct use, enabling the accurate and passive tracking of inhaler usage. Additionally, without adding to the workload of patients or healthcare professionals, the system detected method flaws, including inadequate inhalation length, guaranteeing adherence to recommended drug schedules. [28] In terms of diagnosis, AI supports the interpretation of pulmonary function tests, a critical yet complex component of asthma diagnosis. This is particularly beneficial for primary care clinicians who may lack specialized expertise, thereby complementing the clinical history and physical examination required for accurate diagnosis. [29]Additionally, ongoing research emphasizes AI's potential in predicting asthma exacerbations and monitoring disease control, often leveraging digital inhaler data to refine predictions and improve management strategies. [30] Electronic Health Record (EHR) use is another transformational application. Artificial intelligence (AI) systems may reveal longitudinal patient data, including clinical history, diagnostic results, and treatments, by using natural language processing (NLP) to extract insightful information from lengthy clinical narratives. Finding disease patterns, tracking results, and improving clinical decision-making are all made easier by this capacity to extract and analyze vast amounts of data. [31] Although there are many chances for integrating AI into asthma care, obstacles like making sure it works with clinical procedures and dealing with the variety of training datasets must be addressed if its full potential is to be realized. These developments open the door for artificial intelligence (AI) to become a key component of asthma treatment, fusing technology with conventional medical procedures to provide better results.[32]

3.2 Adherence monitoring using digital smart inhalers (DSI)

Digital smart inhalers (DSIs) are advanced inhaler devices equipped with sensors and wireless communication technologies, such as Bluetooth to monitor and optimize asthma care. These devices gather comprehensive information on inhaler technique, adherence, and usage, then send it to cloud platforms or mobile apps. In addition to helping patients better manage their conditions, they also give healthcare practitioners the ability to modify treatment regimens as necessary by offering real-time feedback, reminders, and insights about dose trends. They have the potential to improve adherence and decrease hospital visits, which might cover the cost of their deployment, according to a 2017 NICE MedTech briefing. According to the CONNECT2 study, DSIs enhanced asthma

management, decreased the need for relievers by 38.2%, and offered unbiased information on inhalation characteristics such as volume and inspiratory flow.[33] It has been demonstrated that other gadgets, such as smart spacers, greatly lower inhalation mistakes, providing a useful instrument for individualized instruction.[34] Other studies, such as the STAAR research, showed that these devices decreased the incidence of hospital admissions and oral steroid usage in addition to improving adherence, with an average adherence of 70% compared to 49% in controls.[35] Nonetheless, obstacles continue to exist, such as the initial expenses, restricted incorporation into healthcare systems, and privacy issues. [36] Clinicians point to data overload as a possible obstacle to successful deployment, while patients have voiced concerns over large designs and less customization. Notwithstanding these obstacles, DSIs certainly have the potential to enhance asthma outcomes and assist medical practitioners in delivering individualized therapy. As suggested by GINA recommendations and other studies supporting their usage, more research is needed to overcome these shortcomings and establish their place in clinical practice.[37]

3.3 telemedicine

Telemedicine for asthma care has evolved in various forms, including synchronous visits such as Direct-to-Consumer (DTC) and Facilitated Virtual Visits (FVVs), as well as asynchronous options like Remote Patient Monitoring (RPM), mobile health (mHealth) applications, and e-consults. DTC remains the most often used approach since it enables remote monitoring of device-based measurements and the assessment of environmental triggers at the patient's residence. FVVs allow the provider to do physical examinations remotely using tools like digital stethoscopes and spirometers. They are usually conducted at nearby clinics with the assistance of support personnel or telepresenters. Research indicates that FVVs can provide outcomes that are comparable to those of in-person visits; in fact, some studies have found that virtual environments can enhance asthma control scores when compared to in-person treatment.

RPM and mHealth apps are key for improving asthma management outside the clinical setting. Devices such as digital inhalers and peak flow meters can monitor adherence, while mobile apps track asthma triggers and medication usage, potentially improving outcomes such as Asthma Control Test (ACT) scores and reducing medication use. Nevertheless, the FDA does not regulate many of these technologies, and further study is required to confirm their effectiveness. To cut down on wait times and pointless referrals, e-consults—where providers consult experts asynchronously—are also becoming more popular. E-consult and interprofessional consultation billing codes facilitate these online exchanges and improve care coordination between specialists and primary care physicians. Despite these developments, obstacles including internet availability, digital literacy, and reimbursement concerns still exist. For telehealth to be implemented as effectively as possible, a strong infrastructure and ongoing evaluation are necessary.[38]

Figure 1: A Digihaler is a contemporary, small inhaler that tracks medicine administration using an integrated digital sensor. With a flip-top mouthpiece and a little display for use statistics, it has a stylish appearance[39].

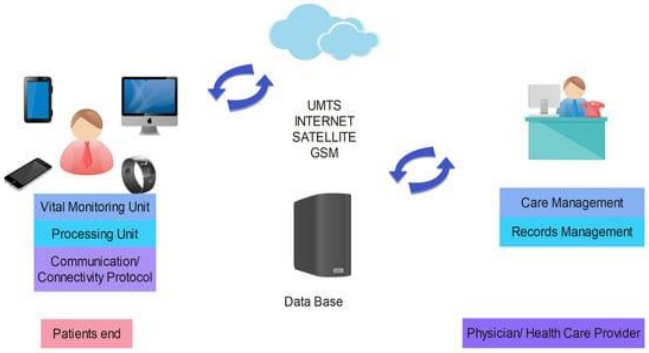

Figure 2: shows the Telemedicine for asthma care[40].

4. CONCLUSION

Asthma continues to be a complex and heterogeneous disease that presents significant challenges for both diagnosis and treatment. The diversity in its clinical presentations, phenotypes, and underlying molecular mechanisms necessitates personalized care to effectively manage the condition. Advances in diagnostic techniques and a deeper understanding of the disease's pathogenesis have led to more targeted and effective treatments, such as biologic therapies that address specific inflammatory pathways. Anti-IgE, anti-IL-5, and anti-IL-4/IL-13 therapies offer hope for patients with severe and difficult-to-control asthma, improving disease outcomes and reducing reliance on traditional corticosteroid therapies.

Moreover, technological innovations, such as artificial intelligence and digital smart inhalers, are transforming asthma care by improving monitoring, adherence, and personalized treatment strategies. AI's role in predicting exacerbations, optimizing medication administration, and analyzing vast healthcare data sets is enhancing clinical decision-making and the overall patient experience. Telemedicine also shows promise in making asthma care more accessible and efficient, particularly for remote

populations, though logistical challenges such as infrastructure and digital literacy must be addressed for its full potential to be realized.

In conclusion, while significant strides have been made in understanding asthma and improving its management, ongoing research, and technological integration are essential for optimizing patient outcomes. By incorporating these novel approaches, the future of asthma care looks promising, with a greater focus on precision medicine and patient-centered treatment strategies that can adapt to the unique needs of each individual.

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