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Approaches to the Control and Management of Asthma in the Modern Era: A Review of the Literature

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Abstract:
Asthma is a prevalent chronic illness necessitating frequent clinic appointments and possible hospitalisations. The spectrum of sickness is diverse and may fluctuate over time. In recent decades, it has been increasingly evident that asthma is not a singular disease but rather a syndrome comprising numerous phenotypes and endotypes; therefore, a universal treatment strategy may not be suitable for all people. Every asthma exacerbation should be seen as an acute pulmonary event, necessitating measures to mitigate future occurrences by suitable interventions. After an exacerbation, one can prevent future episodes by evaluating adherence and enhancing asthma management. Thorough inquiry will enable physicians to discern asthma triggers and impediments to effective asthma management, as well as comprehend health beliefs or socioeconomic challenges that may have precipitated the acute episode. Novel therapeutics utilising nanotechnologies for asthma are currently available. Recent advancements in nanoscience and medicine have facilitated the development of inhalable nanomedicines that can improve efficacy, patient adherence, and quality of life for those with asthma. This article examines new study findings in the field of nanotechnology and asthma treatment. Currently, we possess digital technologies that can facilitate an improved precision medicine approach to the management of respiratory diseases and enhance shared decision-making. Additional efforts are required to enhance the adoption of digital devices and incorporate their utilisation into individualised asthma and COPD care. In the contemporary period, these methodologies represent the most convenient and effective future outlook for the care of asthma and other respiratory problems.

Keywords: Asthma, COPD, Nanoscience, Nanomedicines, Nanotechnologies.

1. Introduction:

Asthma is a chronic respiratory condition affecting the airways, characterised by significant healthcare resource utilisation, productivity loss, and diminished quality of life. It impacts approximately 300 million individuals worldwide and is responsible for 300,000 fatalities annually [1]. Asthma is a chronic condition that impacts both children and adults. Inflammation and muscle constriction around the small airways lead to narrowing of the lung air passages. This results in asthma symptoms including cough, wheezing, shortness of breath, and chest tightness. The symptoms are intermittent and typically exacerbate at night or during physical activity [2]. Asthma remains frequently under-diagnosed and under-treated. Effective management necessitates accurate diagnosis, assessment of severity, appropriate medication, patient education, a written action plan, continuous monitoring, and suitable follow-up [3].
The heterogeneity of asthma is increasingly acknowledged, underscoring the necessity for personalised medicine and the advancement of targeted therapeutic strategies [4]. The characteristics of asthma include chronic airway inflammation, variable airway narrowing, and airway hyperresponsiveness (AHR) to both specific and nonspecific triggers, along with structural changes in the airways known as airway remodeling [5]. Innovative technology can personalise management strategies using real-time individualised data. Numerous digital strategies have been established to assess and enhance adherence to inhaled medications and the associated techniques [6].

2. ETIOLOGY AND PATHOPHYSIOLOGY OF ASTHMA

2.1. Etiology:

2.1.1. Rhinovirus infections and their roles in asthma

Rhinovirus infections are capable of inducing wheezing illnesses across all age demographics. Rhinovirus infections commonly trigger acute wheezing illnesses in preschool children. Children exhibiting wheezing in conjunction with rhinovirus infections face an elevated risk of subsequently developing asthma. Following the onset of asthma, rhinovirus infections serve as significant triggers for acute airway obstruction and exacerbations in both children and adults. Rhinovirus infections typically induce cold symptoms in most individuals, with minimal or no impact on the lower airways [7].

2.1.2 Genetics involved in allergy and asthma

Examples of conditions lacking a traditional Mendelian inheritance pattern but possessing a clear genetic propensity include asthma and allergic illnesses. Multiple interacting genes, some of which have protective properties and some of which contribute to the development of disease, interact to generate these "complex" genetic disorders. Each gene has a varying tendency to be expressed. Furthermore, for these illnesses to manifest, suitable environmental triggers must exist. Performing a genome-wide search, which identifies the location of the disease-causing gene on a human chromosome and then identifies neighbouring genes that may be relevant, is one method of determining the genetic basis for these illnesses. Assessing abnormal structure or regulation within genes known to be implicated in asthma and allergies is an alternate method for determining heritable components of these conditions [8].

Finding areas of variable DNA methylation across cohorts has been the main focus of EWAS, which examines the connection between epigenetic changes and characteristics. This could help to explain trait susceptibility that GWAS is unable to detect. Crucially, environmental factors including air pollution and dietary components can affect the epigenome, specifically DNA methylation. 68 Therefore, the totality of these outside environmental factors (often referred to as the "exposome") may significantly impact asthma susceptibility. It is crucial to remember that epigenetic changes vary depending on the type of cell, hence caution should be used when interpreting EWAS results [9].

2.1.3 Triggering factors [10]

Viral Infections: Clinical analysis showed that a viral upper respiratory infection was the cause of an asthma attack in 40% of children. The child's parents noted that the child had a cough and rhinitis, either with or without a fever.

Season: It has long been known that asthma attacks vary seasonally. Compared to the summer and monsoon seasons, allergy symptoms have been recorded more commonly throughout the winter.

Food: The relationship between food allergy and asthma has been a contentious topic, with various dietary triggers eliciting allergic reactions in different individuals.

Aeroallergens: Research indicates that children exhibit increased sensitivity to indoor allergens as they age in such environments.

Irritants: Smoke, sprays, the burning of mosquito coils, and cooking odours are significant triggering factors, particularly for children.

Air pollutants: Air pollutants exist in both outdoor and indoor environments. Key outdoor pollutants include black smoke, total suspended particulates (T.S.P), sulphur dioxide (SO_2), nitrogen oxides (NO_2), carbon monoxide (CO), ozone (O_3), and lead, which are generated by the combustion of fossil fuels, industrial activities, mining, paper pulp production, and automobile emissions.

Dust mites: Dust mites are estimated to contribute to 50 to 80 percent of asthma cases, in addition to numerous instances of eczema, hay fever, and other allergic conditions. Symptoms typically manifest as respiratory issues, including sneezing, itching, watery eyes, and wheezing.

2.3 PATHOPHYSIOLOGY AND UNDERLYING MECHANISM IN ASTHMA:

Asthma and chronic rhinosinusitis (CRS) are prevalent, often concurrent disorders located at the distal extremities of the respiratory system. They are linked by common underlying systems that react to certain biologics [11].

During the 2000s, asthma was categorised into two main endotypes: Th2 and non-Th2 asthma. The classification was determined by the presence or absence of (i) CD4+ T-helper cell type 2 (Th2)-mediated inflammatory responses (IL-4, IL-5, and IL-13) or Th17-mediated responses (IL-17, IL-1β, IL-23), (ii) IgE, and (iii) increased levels of eosinophils, neutrophils, basophils, and mast cells in the airways [12]. The recent identification of type 2 innate lymphoid cells (ILC2s) and subsequent studies emphasising their significant role in the production of hallmark type 2 cytokines have prompted a revision of terminology, categorising asthma as type 2 (T2) and non-type 2 (non-T2), also known as T2-high or T2-low [13].

T2 asthma: The airway epithelium in individuals with T2 asthma demonstrates heightened production of pro-inflammatory cytokines and mediators, including alarmins such as IL-25, IL-33, and TSLP, as well as IL-6, IL-8, IL-

1α/β, RANTES, and TNF, in response to environmental stimuli. The mediators create a localised pro-inflammatory microenvironment that promotes the activation, recruitment, and functionality of additional immune cells within the local tissue or those drawn from the bloodstream. [14-16]

Non-T2 asthma: Non-T2 asthma, also known as type 2-low or non-eosinophilic asthma, is a heterogeneous condition characterised by diverse underlying mechanisms. The mechanisms may involve the influx of CD4+ type 1 T helper (Th1) and type 17 T helper (Th17) cells, type 1 and type 3 innate lymphoid cells (ILC1 and ILC3), neutrophils, and increased levels of pro-inflammatory mediators in lung tissues, including IL-1ß, IL-6, IL-8, IL-17A/F, IL-22, IFN-γ, and TNF-α. Studies suggest that an imbalance between Th17 and Treg cells may play a role in corticosteroid-resistant neutrophilic asthma [17-18].

3. MANAGEMENT AND CONTROL OF ASTHMA:

The principal approach to asthma management is inhalation, which constitutes the cornerstone of pharmacotherapy. The direct injection of the medicine into the airways, utilising optimal quantities, results in minimum side effects when used correctly. Administering aerosolised medication to children has difficulty in attaining deposition in smaller airways, underscoring the necessity for the precise medication and suitable apparatus. The extensive array of drugs and equipment can confound clinical decision-making. Clinicians managing paediatric asthma must possess a comprehensive awareness of the various inhaled medicines and devices, as this knowledge is essential for selecting the optimal treatment for each patient [19].

Asthma remission: Remission does not equate to a cure. The remedy necessitates the reinstatement of airways to their standard pathological condition, along with a prolonged absence of symptoms, generally without the need for continuous treatment. Assessing asthma status is essential for determining remission. Essential variables encompass the examination of asthma symptoms and exacerbations, in addition to the assessment of pulmonary function and underlying pathology [20].

Historically, asthma therapy has encompassed the administration of anti-inflammatory agents and bronchodilators [21]. The combination of inhaled corticosteroids (ICs) with formoterol for reliever therapy markedly reduces the risk of exacerbations compared to short-acting beta-agonists(SABA). Currently, there are two categories of drugs employed in asthma management: rescue medications and controller medications [22]. Rescue drugs are employed to swiftly relieve symptoms (within minutes), whilst controller meds are taken every day to manage all asthma symptoms and achieve asthma remission [23-24]. Presently, some novel strategies have been formulated, which will be elaborated upon below:

3.1 Biologics:

Biologics, particularly humanised monoclonal antibodies, precisely target molecules associated with the T2 response, therefore blocking this pathway and mitigating asthma symptoms. Biologics for asthma management target specific molecules: IgE (omalizumab), IL-5 (mepolizumab and reslizumab), the IL-5 receptor (benralizumab), the IL-4/IL-13 receptor (dupilumab), and TSLP (tezepelumab) [25]. Biologics constitute a targeted therapy approach for eosinophilic asthma, exhibiting considerable promise for attaining clinical remission in select individuals [26-27].

3.2 Monoclonal antibodies as promising therapy for asthma:

The transformative advancement in asthma occurred in 2003 with the introduction of the first biological therapy for severe asthma: the anti-IgE monoclonal antibody omalizumab. The FDA has approved omalizumab, mepolizumab, benralizumab, reslizumab, dupilumab, and tezepelumab for the treatment of severe asthma.

3.3 Personalized medicine as future approach for asthma therapy: Research into novel pharmacological treatments for severe asthma continues to be vigorous, with numerous potential paths being explored. Alongside the advancement of novel pharmaceuticals, efforts are underway to enhance the utilisation of current medicines and to get a deeper comprehension of their mechanisms. A viable avenue is identifying biomarkers indicative of response to a particular monoclonal antibody, a crucial element in therapy personalisation, while another focusses on enhancing asthma phenotyping, thereby facilitating the selection of a medicine aligned with the immunological profile.

3.4 Nano Drug Deliveries for Targeting Asthma:

Recent advancements in science and technology have established nanotechnology as a feasible platform for enhanced disease detection and treatment [32-33]. The development of artificial nanoparticles (NPs) presents a potential solution to address significant challenges in standard therapeutic approaches [34].

3.5 Lipid-Based Nanoparticle

3.5.1 Liposomal NPs

Liposomal formulations have been proposed as a novel strategy for effective asthma therapy due to their feasibility, biocompatibility, and advantages over conventional formulations currently available [35-36].

Liposomes have garnered interest as a potential alternative to oral administration for the treatment of respiratory disorders such as asthma, due to their noninvasive nature and ability to provide sustained drug release. The application of liposome-based drug delivery to the lungs may enhance drug retention, leading to a reduction in extra-pulmonary adverse effects and an improvement in therapeutic efficacy for asthma treatment.

3.5.2 Polymeric Based Nanoparticles

Nano- suspension: The treatment of ovalbumin-induced asthma can be effectively achieved through a self-nanoemulsifying drug delivery system developed by Cao et al. The self-nanoemulsifying drug delivery system of isoliquiritigenin demonstrated significantly improved bioavailability and anti-asthma efficacy compared to isoliquiritigenin suspensions [37].

3.5.3 Inorganic NPs

(i) Nano-Gold Particles:

Gold, as a widely used nanoparticle, has various medical applications, encompassing diagnosis, therapy, and imaging techniques. This results from its distinctive properties, including a considerable contact surface area relative to its volume. Gold nanoparticles present various advantages compared to other nanoparticles, such as their neutral characteristics, stability, high diffusion capabilities, non-toxicity, environmental compatibility, and ability to alter their optical properties [38].

(ii) Nano Vaccine for Asthma: Furthermore, the exploration of nanoparticle-based immunotherapy targeting specific antigens associated with asthma represents a promising avenue for research. Researchers have identified a method to prevent and treat dust mite allergies through the application of a vaccine utilising nanoparticles [39].

3.6 Electronic Monitoring Devices to Support Inhalation Technique in Patients with Asthma

Electronic monitoring devices (EMDs), referred to as digital or smart inhalers, possess the capability to objectively assess and enhance patient adherence to therapy through feedback mechanisms. New-generation EMDs offer real-time feedback regarding the patient's inhalation technique. Scientists have developed specific devices that are capable of measuring inhalation techniques.

CapMedic®; Digihaler®; Hailie Sensor®; INhaler Compliance Assessment™; Respiro®; and Smart AeroChamber®.

1. The CapMedic® device is a sensor currently only attachable to pMDIs. Often pMDIs are used in combination with spacers or valved holding chambers to reduce problems of poor inhalation technique with pMDI alone. Therefore, the GINA guidelines recommend the use of pMDIs with spacers **[40-41].**The device is rechargeable, and a full battery lasts for approximately 200 inhalations, or about 100 days of use, assuming two inhalations and lung function assessment tests daily with the same device

2. The Digihaler® application allows patients to receive messages and reminders through the application. Data on inhaler use can be displayed on a smart phone screen during an HCP visit or as a portable document format (PDF) summary. The device cannot be recharged and has a battery life that surpasses the in-pouch shelf life of the inhaler device [42].

4. Approaches to implement innovative advance inhaler technology:

Inhaled medications play a central role in the management of asthma conditions for most patients. Global recommendations highlight the importance of adherence to inhaled medication and correct inhalation technique in managing symptoms.

A variety of digital strategies have been developed to monitor and improve inhaled medication adherence and technique. A recent Cochrane review by Chan et al investigated the range of digital interventions available to address medication non-adherence, highlighting their potential to improve clinical outcomes in patients with asthma compared with non-digital interventions and usual care. Digital inhalers can provide greater connectivity between patients and clinicians through the sharing of personalized data. Information on medication adherence and/or technique is transferred between connected devices, such as inhalers and smartphones via mobile application services [43-44]. To realize the full potential of digital inhalers, further innovation is needed to advance research as well as our understanding of respiratory disease and the patient's role in managing it [45].

4.1 Mobile-based asthma clinical decision support system for asthma management:

For the past 20 years, the Global Initiative for Asthma (GINA) guideline has been issued for doctors as a framework for managing asthmatic patients based on the most recent data [46]. Consequently, this expert system may provide the GINA suggestions to users via a user-friendly application that requires no third-party solutions and is free from temporal and spatial constraints. Furthermore, all asthmatic patients must own a personalised written asthma action plan to enhance asthma management efficacy [47-48]. Our Clinical Decision Support System (CDSS) may furnish healthcare providers with an automated, personalised action plan by integrating patient data with the incorporated knowledge from the GINA standards. The application's interactive design will assist young physicians and medical students in utilising it as an instructional tool for self-training [49].

4.2 Imaging based biomarkers in asthma management: Imaging biomarkers may be important in delineating distinct phenotypes and in predicting and/or evaluating therapeutic responses, akin to the paradigm of T2-targeted biologics for individuals with the T2-high asthma phenotype. Imaging biomarkers, being non-invasive, may significantly contribute to both research and clinical practice.

4.3 Computed tomography and quantitative imaging:
In acute circumstances, a CT scan is typically conducted when the chest x-ray results are ambiguous or there is a significant suspicion of a pathology alongside an asthma exacerbation. Pneumothorax, pneumomediastinum, and pulmonary infections can be easily identified using chest CT. Additionally, CT is utilised for the evaluation of both major and minor airway pathology. Thickening of the bronchial wall, bronchiectasis, and mucus plugging are indicators of big airway disease in asthma, but may also signify underlying infection conditions such as allergic bronchopulmonary aspergillosis.

4.4 MRI
Lung MRI is regarded as difficult because to the low proton density of lung tissue, rapid signal decay, and respiratory artefacts; yet, it may serve as a radiation-free alternative to CT scans. To far, MRI in asthma is primarily utilised in a research context. The spatial resolution of MRI is inferior to that of CT, however it can offer dynamic information. Patients with severe asthma exhibit respiratory abnormalities on MRI, which correspond with LAA on CT [50-53]. The degree of breathing abnormalities observed in MRI correlates with asthma exacerbations and other clinical indicators of asthma severity [54]. Ventilation imaging is clinically significant in characterising asthma and may serve as a supplemental tool in assessing difficult-to-manage asthma in a clinical environment [55].

5. Future perspectives for asthma management:

Scientists are developing innovative methods such as nanotechnology, monoclonal antibodies, electronic devices, and mobile applications for digital asthma monitoring to enhance asthma control and treatment. In the forthcoming days, systems such as Artificial Intelligence (AI) may assume a pivotal position in asthma control. Therefore, developing creative strategies is the future objective for asthma management.

5.1 Artificial Intelligence (AI):
Artificial intelligence is being integrated into clinical research and everyday practice. When combined with extensive, well-characterized datasets, it produces models that enhance patient care and research. In chronic and prevalent conditions like asthma, AI may play a significant role in routine patient management [56].
It is essential to acknowledge that AI is not yet fully advanced in quantitative imaging tasks. This pertains to multiple concerns, including specialised hardware, software, PACS systems, biases in training datasets, a scarcity of high-quality annotated data and research, and ethical dilemmas related to accountability for misclassifications. In asthma imaging, AI can enhance imaging techniques and elevate image quality across modalities like CT and MRI, while also being analysed by machine learning algorithms to provide biomarkers. Diagnostic imaging is the predominant data source utilised in healthcare applications of AI. [57]
In asthma, additional research is required to integrate imaging data with clinical and genomic information to discover asthma phenotypes that may be more responsive to particular treatments. Furthermore, imaging ought to be incorporated into AI-driven decision trees for asthma control.

5.2 Disease modifying effects of biologicals: There is growing evidence that biologic therapy aimed against type-2 immunity exert disease-modifying effects, especially on small airway remodelling [58]. Current research is evaluating biologic therapies, including tezepelumab (NCT05280418) and benralizumab (NCT03976310), in relation to imaging outcomes and distinct asthma sub-phenotypes (e.g., luminal mucous blockage, airway remodelling) [59].
5.3 Novel immunotherapy strategies: Molecular allergology; The majority of allergens found in common inhalants and foods have been successfully cloned. This has facilitated accurate molecular diagnosis of IgE sensitivities to predominant allergens (identified by over 50% of persons) and minor allergens, as well as the detection of cross-reactive epitopes of diminished clinical significance [60].
5.4 DNA-based vaccines. In mouse allergy models, DNA-based vaccinations increased TH1 and Treg cell responses and decreased TH2 cell responses. Their repeated use in humans is limited by the theoretical risks of plasmid DNA incorporation into the human genome causing carcinogenesis, development of anti-DNA antibodies, and long-term allergen persistence causing widespread IgE triggering and anaphylaxis [61].

6. Conclusion

The education of asthma management and prevention by healthcare professionals is a crucial responsibility. It is essential to focus on the hospitals at the basic level. By mobilising health care systems and professionals, along

with ensuring access to appropriate medications, it is feasible to alleviate the burdens linked to severe or uncontrolled asthma. Significant advancements in technology have been effectively integrated into inhaler devices, offering a range of digital solutions that could transform disease management and improve outcomes. Digital inhaler devices connected to mobile applications can facilitate modifications in patients' behaviours and attitudes regarding the management of their asthma or COPD. The future outlook for asthma management should emphasise the adoption of electronic and more user-friendly digital methods for effective asthma care. The research objectives should focus on targeted therapy utilising monoclonal antibodies or more effective nano-level therapeutic formulations, accompanied by innovative delivery systems that minimise the adverse effects associated with various drugs.

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