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Review

Progress in diagnosis and treatment of difficult-to-treat asthma in children

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***Abstract*:** At present, medications containing inhaled corticosteroids (ICS-containing) are the keystones of asthma treatment. The majority of asthmatic children can significantly improve clinical outcomes with little worsening by standardized inhaled glucocorticoid treatment, but there is still a small proportion of children who are unable to achieve good symptom control even after the maximum standardized treatment, known as 'children with difficult-to-treat asthma (DA)'. The high heterogeneity of DA makes therapy challenging and expensive, which poses a serious risk to children's health and makes it extremely difficult for clinical physicians to accurately identify and treat children with DA. This article reviews the definition, evaluation, and treatment of this asthma in order to provide a reference for optimal clinical decision-making.

Keywords: children, diagnosis and evaluation, difficult-to-treat asthma, treatment

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Introduction

Asthma is a heterogeneous disease characterized by chronic airway inflammation and airway hyperresponsiveness. Its clinical symptoms mainly include wheezing, shortness of breath, chest tightness, and/or coughing. Asthma is a serious public health issue worldwide. It impacts between 1% and 18% of the population in different countries.[1] It is reported that there are about 300 million people worldwide who suffer from asthma. With the increase in urban population, it is expected to reach 400 million in 2025.[2]

Among children, asthma is one of the most common chronic diseases. It is among the top 20 diseases worldwide in terms of disability-adjusted life years in children.[3] The International Study on Asthma and Allergy in Children (ISAAC) found that the prevalence of asthma in children has increased significantly around the world, affecting 13.7% of 13 to 14-year-olds and 11.6% of children aged 6–7.[4,5] In China, children living in urban areas had an asthma prevalence of 3.02% overall.[6] Despite significant advancements in the diagnosis and management of pediatric asthma in China, more than 20% of these patients do not have their asthma under good control.[7] Globally speaking, asthma management and control are typically insufficient, especially in areas with low resources.[8]

Difficult-to-treat asthma (DA) is characterized by persistent symptoms despite the use of basic asthma management. The causes can be multifactorial, including diagnostic errors, poor adherence to therapy, environmental and social factors, comorbidities, and psychological factors.[9,10] Although it affects only a small proportion of the population (about 3–10%).[11] DA imposes a high morbidity rate with significant social burden and healthcare resource utilization.[12,13] Indeed, the medical expenses of children with DA account for 30–50% of the total medical expenses of all asthmatic children.[14] Beyond the financial cost, DA patients' quality of life and academic performance might suffer dramatically because of the increased risk of exacerbations and hospitalization.[15,16] It is anticipated that actively researching efficient treatments for this type of asthma will lessen the significant burden of asthma symptoms worldwide.[17] In this review, we summarize the latest research on the definition and treatment strategy of DA.

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Definition of relevant concepts

Severe asthma and problematic severe asthma

Although severe asthma has many definitions at different stages, the differences between them are subtle.[1,18–20] According to the American Thoracic Association and the European Respiratory Society, severe asthma is defined as requiring treatment with high dosage inhaled corticosteroids (ICS) together with a second controller and/or systemic corticosteroids to keep it from becoming 'uncontrolled' or that does so even after receiving this medication.[21]

The concept of 'problematic severe asthma' was put forward in 2008.[22] It is now used as a catch-all phrase to refer to kids receiving high-intensity treatment (Global Initiative for Asthma steps 4–5) but still experiencing poor asthma control (frequent exacerbations, enduring symptoms, or both). According to the influencing factors, it is divided into three subgroups: DA, severe therapy-resistant asthma (STRA), and refractory difficult asthma (RDA).[23,24]

Although they are defined differently, both the definition of severe asthma and the concept of 'problematic severe asthma' are based on the level of treatment and symptom control. Nowadays, accurate diagnosis and treatment of childhood asthma are becoming increasingly important. Therefore, it is more appropriate to refer to children whose symptoms are still poorly controlled after a period of high-intensity standardized treatment as having 'problematic severe asthma'. This type of asthma can be further subdivided into different categories based on whether the influencing factors are reversible or not, allowing for more targeted interventions and treatments.

Difficult-to-treat asthma

DA is caused by the failure of basic asthma management due to potentially changeable factors (figure 1). When these factors are optimized, the symptoms of children can be better controlled. DA is a subset of problematic severe asthma; a study by the Royal Brompton Hospital in the United Kingdom, using nurse-led home visits to assess children's problematic severe asthma, revealed that, following initial assessment, more than 50% of children with problematic severe asthma are classed in the DA group.[25] A Swedish study looked at a group of children who had problematic severe asthma and discovered that 39% of them had challenging asthma.[26] These earlier researches have demonstrated that DA contributes significantly to troublesome severe asthma. Therefore, it is clear that a deeper comprehension of this high-risk population is needed in order to improve our classification of severe asthma sufferers.[27]

In the 2020 recommendations for the diagnosis and treatment of childhood bronchial asthma in China, children's 'DA' refers to asthma that has not been adequately controlled despite being treated with a combination medication regimen that includes medium dosage ICS.[28] According to this assertion, the definition of DA in China differs from that in the rest of the world. Nevertheless, the guidelines underlined the significance of studying the pertinent elements of children's DA, including asthma diagnosis, adherence to medicine, comorbidity, environment, and psychological factors, and pointed out that for children with difficult-to-control asthma, it is vital to eliminate the aforementioned components in combination with children's symptom control level and the evaluation of the therapeutic effect of drugs in use. Finally, determine whether it is STRA.

Meanwhile, there is a pronounced sex disparity in asthma. Although boys under the age of 13 have a higher prevalence of asthma, adult women have higher rates of the condition than do men.[29] Likewise, women have stated that their adult asthma symptoms have become more severe, and more likely to develop into DA. There are many reasons for this gender difference. In childhood, boys have more significant dysanaptic lung development compared to girls and a mismatch between the size of the airway tree and lungs in relation to airway flow rate.[30]

The shift in disparities in asthma prevalence between sexes from childhood to adulthood is mostly mediated by sex hormones. And adolescence is when these changes take place.[31] Furthermore, other researchers discovered that the presence of female sex hormones in vivo was vital for enhancing Th17 cell development in vitro.[32] Moreover, female mice had considerably greater amounts of eosinophils in bronchoalveolar lavage fluid (BALF) in comparison with males in an ovalbumin (OVA)-induced asthma model, and ovariectomy has been demonstrated to reduce the

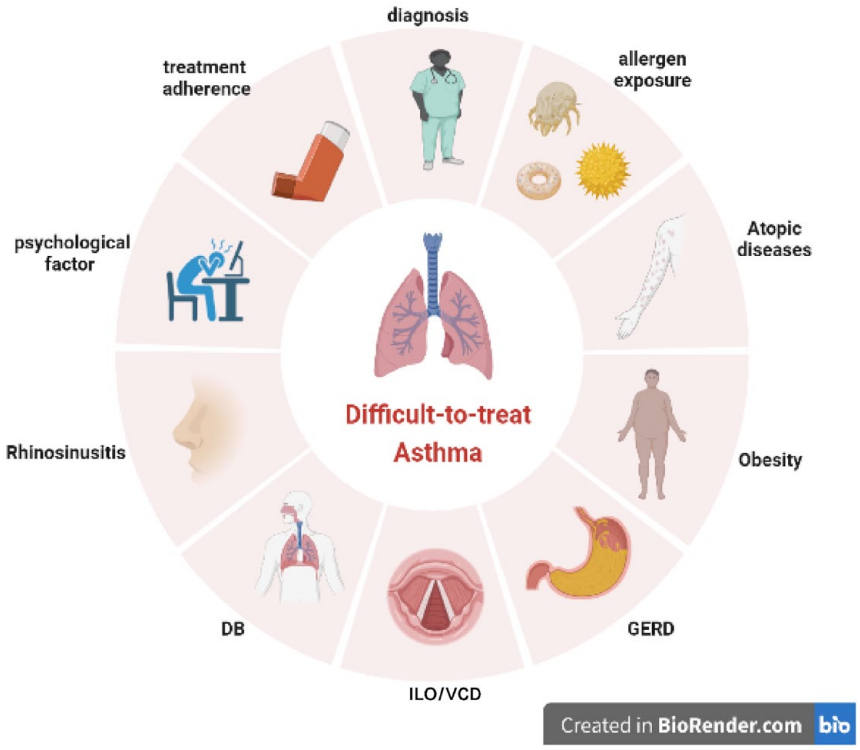

Figure 1. Major factors affecting difficult-to-treat asthma.
Source. This original figure was created by the authors using 'BioRender.com'.
DB, dysfunctional breathing; GERD, gastroesophageal reflux disease; ILO/VCD, inducible laryngeal obstruction (formerly known as vocal cord dysfunction).

level of eosinophils in BALF when compared to sham-operated controls after OVA challenge.[31]

Severe therapy-resistant asthma

Despite efforts to address modifiable factors, such as improving adherence to high-dose ICS and reducing exposure to allergens, the symptoms of STRA often remain poorly controlled in children. The underlying mechanism of glucocorticoid resistance in these children is not fully understood, but research suggests that oxidative stress and Th2-related pro-inflammatory cytokines play a major role.[33,34] Unlike adults with STRA, children with this condition typically have airway remodeling and fluctuating levels of eosinophils, but do not exhibit increased levels of neutrophils.[35] In fact, the vast majority of kids with STRA (85%) will test positive for one or more allergens, have very serious and intricate allergen sensitivity, and typically have more drastic disease states when there are also food allergies present.[36,37] Such children may require care that goes beyond standard treatment guidelines.

Untreated severe asthma and RDA

The World Health Organization, which considers that severe asthma encompasses three groups: untreated severe asthma, DA, and STRA, was the organization that initially presented the idea of 'untreated severe asthma'.[38] After ongoing development, serious asthma that's left untreated is described as having been brought on by a missed diagnosis or a dearth of treatment options.[39] This type of asthma is not only common in nations with low or intermediate incomes but also exists in high-income countries due to various political factors.[40] In addition, in some countries, the word 'asthma' is considered to have a stigma. This misunderstanding leads to an unwillingness to accept the diagnosis, which affects the treatment of asthma.[8]

RDA is considered a potentially modifiable factor that has been identified, but it is difficult for children to manage. Biotherapy should be taken into account for these children with severe or RDA, as they are at risk of serious and potentially fatal asthma episodes.[24]

The possible mechanism related to DA

Type 2 immune responses

Proteases derived from complex allergen sources, such as house dust mites, cockroaches, and fungi (*Aspergillus fumigatus, Alternaria alternata*), have been demonstrated to destroy and stimulate airway epithelial cells.[41,42] Numerous mediators, cytokines, and alarmins, including IL-33, thymic stromal lymphopoietin (TSLP), and IL-25, are secreted by activated epithelial cells. It has been established that IL-33, IL-25, and TSLP play key roles in mediating the worsening of asthma.[43] And they can activate type 2 innate lymphoid cells (ILC2) in the airways, which can then trigger the release of effector molecules including IL-4, IL-5, and IL-13 to cause a non-allergic eosinophilic inflammatory pattern.[24]

Non type 2 immune responses

Recent research has revealed that Th1 and Th17 cells are also essential to the pathophysiology of severe asthma. interferon-gamma (IFN-γ) and the downstream cytokines CXCL9 and -10, as well as the macrophage/dendritic cell transcription factor IRF5, have all been linked to type 1 (T1) inflammation and have been found to be higher in severe asthma.[44] Increased T1 immunological response (IFN-γ) in the respiratory tract of severe asthma patients could have caused neutrophil chemotaxis *via* the overexpression of CCR1 and CCR3 on neutrophils.[45] Additionally, it has been noted that IL-17A causes steroid resistance and neutrophilic airway inflammation in children.[14] In children with moderate asthma, levels of IL-17A in sputum, nasal wash, and plasma, as well as levels of circulatory T lymphocytes expressing IL-17, were investigated, and it was hypothesized that IL-17 could be related to asthma severity.[14]

Airway wall remodeling

Tissue remodeling in the airways is caused by epithelial cell dysfunction, goblet cell proliferation, raised airway smooth muscle cells, basal membrane strengthening, developed neovascularization in the sub-epithelial cell layers, and a greater accumulation of various extracellular matrix elements.[46] In severe asthma, the epithelium is thicker than in mild-moderate asthma, pro-inflammatory substances are released more frequently, and there is greater proliferation and apoptosis.[47] Remodeling has been connected to histones and DNA methylation in adult asthma. There is growing recognition that epigenetic conditions early in life and throughout embryogenesis have long-lasting effects on DNA and histone methylation, microRNA expression, and cellular activity, all of which are relevant to childhood asthma and influence the emergence and growth of childhood asthma.[46] Submucosal eosinophilia is also linked to pathways of airway remodeling and cellular inflammation. Both the matrix metalloprotease 10 (MMP10) and the mesenchymal to epithelial transition factor (MET) genes probably have a significant impact on these procedures. According to this research, MMP10 and MET were potential motivators for airway wall remodeling.[48] Airway wall remodeling can cause the airway lumen to narrow, and in severe situations, it can result in patients experiencing the signs and symptoms of chronic persistent airway obstruction.

Other pertinent mechanisms

A tiny percentage of people with severe asthma do not respond well to glucocorticoids, and the specific mechanism is not yet fully understood. However, this is linked to immunological dysfunction, genetics, and environmental variables. Changes in glucocorticoid receptors and overactivation of transcription molecules may trigger glucocorticoid resistance.[49]

On the other hand, viral respiratory tract infections continue to have the strongest association with childhood asthma aggravation. Among respiratory viruses, rhinovirus is the most important and common virus that exacerbates asthma.[50] Asthma patients may have deteriorating asthma symptoms as a result of the functional interplay between viral pathology and asthma pathology.[51] Recurrent asthma inflammation may hinder the body's ability to mount an efficient antiviral defense, worsening the virus's already-present airway destruction. Moreover, a viral illness may make an asthmatic's airways more sensitive to triggers like allergen exposure.[51] Interferons (IFNs) are an important family of antiviral cytokines. In patients with asthma, damage to bronchial epithelial cells and plasmacytoid dendritic cells can lead to decreased expression of IFNs,[52] making them more susceptible to viral infections while the antiviral immune response is weakened. Furthermore, long-term use of inhaled glucocorticoids to treat asthma may have immunosuppressive effects, which can accelerate viral

replication, delay virus clearance, and increase the risk of reinfection.[53] Children with asthma may experience delays in the resolution of their symptoms following a viral respiratory infection, which can ultimately lead to disease exacerbation.

Evaluation and management of DA

Validate the asthma diagnosis

If a child's asthma symptoms remain uncontrolled despite treatment with the maximum doses recommended by guidelines, clinicians should highly suspect the diagnosis of asthma. Previous research has discovered that up to 50% of children evaluated for problematic severe asthma have been misdiagnosed or have an affiliated diagnosis.[37] Additionally, 12–30% of non-asthmatic conditions were misdiagnosed as uncontrolled asthma.[21,54]

In order to support a diagnosis of asthma, two key criteria should be met: (1) recurrent airway inflammation produced by exercise, contact with respiratory viral pathogens or specific antigens in sensitized children, and (2) airflow obstruction that is entirely or partially reversible with the administration of inhaler short-acting β-2-agonists (SABA), support the diagnosis of asthma.[55]

The clinical diagnosis of asthma should be based on detailed medical history, combined with physical examination results and objective examination evidence. The medical history must be thoroughly reviewed when reevaluating the diagnosis, with particular attention paid to the symptoms of coughing, wheezing, shortness of breath, and chest tightness; their occurrence frequency, precipitating factors, severity, and accompanying symptoms; previous treatment plans and responses to treatment; a thorough physical examination again; and a reevaluation of the child's prior examination results.[56–58]

If necessary, skin prick testing, total immunoglobulin E (IgE) in serum, and repeat specific radioallergosorbent tests are used to determine a child's atopic status. The increase of eosinophils in blood analysis also helps to support the diagnosis of asthma.[59] A pulmonary function examination was carried out on children to determine the extent of airflow limitation, reactivity to bronchodilators, lung volume, and air retention, among other things.[60] To help establish the diagnosis, it is necessary to find proof of adjustable airflow blockage with a strong bronchodilator response (adults: increase in FEV1 of $>12\%$ and >200 mL; children: an increase in forced expiratory volume in one second (FEV1) from baseline of $>12\%$ is predicted) or to carry out a methacholine or histamine challenge that demonstrates airway hyper-reactivity.[1] Measurement of fractional exhaled nitric oxide (FeNO) is recommended to determine the severity of the disease and adherence to prescribed treatment. In children, FeNO ≥ 35 parts per billion (ppb) are interpreted as indicators of bronchial inflammation.[61] Measurements of FeNO and blood and stimulated sputum eosinophilia analysis can be used to noninvasively imply the existence of airway inflammation that is indicative of specific asthma phenotypes.[62]

Making the distinction between DA, RDA, and STRA is the next stage for problematic severe asthma after getting a confirmed diagnosis of asthma.

Assessment of treatment adherence

Subpar adherence has a well-known negative effect on asthma control and morbidity linked to asthma. It is probably the most significant cause of inadequate asthma control in children and is linked to 80%[63] of asthma deaths. Therefore, a complete assessment of treatment adherence is essential. Excellent adherence is defined as administering the recommended dosages of ICS at a rate of at least 80%,[64] moderate adherence at a rate of 60–80%, and poor adherence at a rate of $<60\%$.[65] How frequently the prescribed medications are taken, as well as how they are taken, are the two key components of the evaluation of treatment adherence.

At first, assess the intake of the prescribed drugs. Studies have indicated that $<80\%$ of the recommended ICS dosages are actually taken by more than70% of asthmatic toddlers. On average, only 14.6% of kids had good adherence.[66] Adherence rates could be much lower in communities or minorities that lack access to necessary medical treatment and public health resources and services.[8] More than 50% of children in the study conducted by Bracken *et al.*[25] had poor prescription uptake ($<80\%$ of recommended dosages)

upon inspection, and 30% of children had only collected fewer than 30% of the prescriptions that had been given to them. Complex factors, such as a lack of parental or teacher monitoring, inadequate medical care services, and a lack of health understanding, contribute to children's poor adherence.[67,68] Since children's or parents self-reports and unbiased evaluations of ICS adherence are rarely in accord, determining how well children adhere to drug use is always challenging.[69] Asthma diaries are written records of asthma symptoms and medication use, usually kept by the child or their parents. These self-reported levels of adherence frequently overstate actual levels. Prescription intake can be measured through prescription records in hospitals or pharmacies to further evaluate the adherence of children to medication. However, it may not be accurate to evaluate adherence only through prescription intake. Good prescription intake does not mean good adherence because the relationship between prescription intake and actual drug use is not proportional. Therefore, adherence can be better assessed by using electronic monitoring devices (EMDs) that are connected to corticosteroid inhalers.[70] Two electronic devices that have been investigated in asthma management are the Nebulizer Chronolog (Medtrac Technologies, Inc, Lake-wood, CO, USA) and the Doser (NEWMED Corp, Newton, MA, USA).[71] The date and time of stimulation are electronically recorded by these machines.[72] Via the measurement of inspiratory flow or audio recordings of proper device usage, several instruments can also evaluate inhaler technique.[73] To combat forgetfulness and unintentional nonadherence, several have audio-reminders.[74] A prospective cohort study using EMDs to monitor drug use adherence in children with asthma demonstrated the clinical usefulness of using objective monitoring tools to assess adherence, which can help distinguish DA from STRA in problematic severe asthma.[75]

Moreover, suppression of FeNO is a straightforward way to forecast how the ICS will react. FeNO is a non-invasive tool used to measure airway inflammation associated with asthma. The higher the FeNO level, the greater the degree of airway inflammation. The FeNO suppression test is used to evaluate the effectiveness of ICS by measuring the reduction in FeNO levels after direct observation of ICS treatment.[76–78] It is possible to identify patients with severe, hard-to-control asthma who respond to ICS but do not adhere to maintenance ICS treatment in subjects with high FeNO (FeNO $\geq$ 45 ppb) by directly observing ICS treatment over a 7-day period.[79,80] Before and after a period of directly observed therapy (DOT) with ICS, FeNO levels are assessed in FeNO suppression tests. Participants in the study underwent a week of remotely monitored, directly witnessed therapy that involved the daily administration of high dosages of ICS. If a 42% drop in FeNO was seen, the FeNO suppression test was positive.[80] For the purpose of evaluating adherence, Heaney *et al.*[79] used remote DOT and FeNO suppression. About half (N = 130) of the 241 people who took the test and completed the research got positive results for suppression. Out of these 130 participants, 89 agreed to continue monitoring for another month. By that time, 64% (N = 54) of the patients had experienced considerable improvements in their symptoms and lung function thanks to effective adherence to long-acting beta-agonist (LABA) and ICS.[81] With the development of computer technology and the application of clinical biological reaction markers, clinicians can gradually objectively evaluate the adherence of children with asthma through the FeNO suppression test to identify DA and then improve the management measures for children with DA.

The second is the assessment of inhalers, including the examination of inhalation equipment and technology. One study found that only 20% of patients visiting specialized clinics had their inhaler technique reviewed, despite the fact that suboptimal inhaler use decreases drug delivery and has a negative impact on asthma outcomes.[82] Modern ICS therapies mandate that the drug be inhaled through a device; ICS should be administered through the Aero Chamber, especially for smaller children. Incorrect inhalation technology and improper equipment use will lead to unsatisfactory deposition of ICS in the airways, which will lead to poor control of asthma symptoms.[83] Less than 50% of kids and their parents or caregivers correctly administer inhaled drugs, according to prior studies.[84] About 40% of children have poor inhalation technology, and 15% of children have used unsuitable equipment.[25] Interventions such as demonstrations can effectively improve children's inhalation delivery technology.[85]

Assessment of the allergen exposure

Continuous exposure to triggers is typical for DA sufferers. One study found that among persons

with DA, 13.7% had experienced exposure to allergens, 23.1% had used nonsteroidal anti-inflammatory medicines, and 6% had smoked.[86] For children, the vast majority of asthma is allergic asthma.[87] Several kids have at least one allergy sensitization, according to earlier studies.[88] Children with DA exhibit greater levels of sensitization and allergy sensitivity compared to those with regular asthma. Furthermore, several researchers discovered that the specific IgE (sIgE) levels and sensitization times had a direct correlation with the ineffective treatment of asthma symptoms.[89] Particularly when combined with viral illnesses and high levels of air pollution, persistent exposure to the suspected allergens can cause poorly managed asthma.[90] Moreover, it has been demonstrated that the chance of an exacerbation is correlated with allergen dose.[91] Therefore, for children with DA, it is important to systematically assess allergen exposure. On this basis, it may be beneficial to reduce children's exposure to allergens as much as possible for effective control of DA symptoms.

At the initial evaluation stage, all children with DA had been evaluated for allergen sensitization. In the follow-up review of exposure, there may be some bias between the parents' report and the actual situation. Home visits led by specialized nurses can correct this bias as much as possible to further determine the allergen exposure of children with DA, such as animal allergens (pet dander, etc.), plant allergens (pollen, ragweed, trees, etc.), indoor dust mites, molds, etc. Meanwhile, under the guidance of specialized nurses, families can take effective measures to prevent or reduce the exposure of children with DA to these allergens. It was challenging to do home visits during the previous COVID-19 pandemic. Also, it made us wonder if, similar to the adherence evaluation, the allergen exposure assessment of children with DA may also be conducted through electronic device perception and recording.

For youngsters of school age, on the other hand, school is where they spend the majority of their time. According to studies, children's exposure to allergens occurs most frequently in the school setting.[92] The level of endotoxin in classroom air often exceeds the recommended adult occupational limit. Children with asthma who had higher symptom scores also breathed air that contained higher levels of endotoxin.[93] It is still highly difficult and expensive to limit children's allergen exposure depending on their school, even though trained nurses can look at children's allergen exposure through school doctors.

Regular or overuse of short-acting β_2-agonists

Regular SABAs use reduces responsiveness and downregulates beta-receptors, which encourages more use. Overuse could also be ingrained.[94] According to the available data, using $\geqslant$3 or more SABA inhaler canisters per year (an average of 1.6 puffs per day) is linked to a higher risk of asthma attacks and a higher chance of being admitted to the hospital or visiting the emergency room, and dispensing 12 or more canisters per year (an average of 6.6 puffs per day) is connected to a higher chance of dying from asthma.[95] The use of SABA nebulizers in particular had a higher correlation with poor asthma outcomes.[96]

Multidisciplinary assessment

After verifying the diagnosis, a thorough multidisciplinary evaluation and care for children with problematic severe asthma should be conducted to separate DA from STRA and further define the direction of treatment adjustment.

Identification of comorbidities

Comorbidities, which can hinder asthma control, are critical in managing children with DA. To comprehensively evaluate children with controlled asthma, identify their comorbidities, and direct the treatment of asthma, it is required to unite multiple disciplines. Atopic diseases, rhinosinusitis, obesity, gastroesophageal reflux disease (GERD), breathing disorders, and vocal cord dysfunction (VCD) are a few of the more prevalent ones.

Atopic diseases. Ineffective asthma management is linked to the occurrence of allergic rhinitis (AR).[97] According to a cross-sectional study, 76% of asthma patients also exhibit symptoms of AR, making it a prevalent related comorbidity among asthma patients.[98] Another cohort research assessing the effects of rhinitis on school-aged children's asthma severity found that AR had a detrimental effect on asthma severity.[99] Some studies have also demonstrated that using intranasal glucocorticoids and recognizing AR in asthmatic children may help regulate the condition.[92] Yet, a randomized, controlled clinical investigation is still required to confirm this finding.

Although there is limited evidence to support a direct link between allergic dermatitis (AD) and food allergies and the severity of asthma, identifying, and managing comorbid allergic disorders in children with asthma may help control the condition more effectively. Firstly, it is common for children with asthma to also have food allergies, and research has shown that asthma may be more severe in school-age children with food allergies.[100] Case–control study found that food allergies are significant risk factors for fatal asthma.[101] Approximately 55% of school-age children with severe asthma have AR, whereas 40% of them have a food allergy, according to the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes.[88] Second, research suggests that allergies to the skin's surface brought on by allergens can trigger a systemic Th2 cell immune response, leading to an increase in serum IgE levels.[102] Many studies indicate that the severity of asthma symptoms is higher in children with AD than in those without. Atopic dermatitis may change how asthma develops.[103] Thus, screening for allergic disorders and providing comprehensive care can help optimize asthma management in children.

Rhinosinusitis. Research has indicated that around 22–45% of patients with asthma also experience chronic rhinosinusitis.[104] This comorbidity may lead to inadequate asthma control, especially in children. Studies have shown that computed tomography (CT) scans of the paranasal sinuses reveal the most significant abnormalities in patients with severe asthma, and treatment outcomes support this finding.[105] Therefore, treating chronic rhinosinusitis, either medically or surgically, can have positive effects on concurrent asthma.[106]

Additionally, there is a potential link between eosinophilic inflammation of the upper airways, including the nasal passages and sinuses, and the development of asthma. According to studies, asthma affects 40–70% of individuals with chronic rhinosinusitis with nasal polyps (CRSwNP), being connected to worse outcomes and more severe sinonasal symptoms. Meanwhile, CRSwNP affects 10–30% of patients with mild asthma and 70%–90% of those with severe asthma.[107] This condition, known as 'united airways disease', suggests that treating rhinosinusitis in patients with asthma may be an effective way of managing the disease.[108] Therefore, clinicians should consider screening for and managing rhinosinusitis in patients with asthma to help optimize asthma control.

Obesity. Numerous studies have found a significant association between childhood obesity and asthma,[109,110] and it is estimated that almost 20% of children worldwide are obese. The odds ratio between overweight or obesity and asthma risk was found to be 1.30 (95% CI 1.23–1.39).[111] The relationship between these two conditions is bidirectional, meaning that obesity can result from asthma, and asthma can also be brought on by obesity.[13] However, in children with asthma, obesity is linked to decreased asthma control and lung function, a lower quality of life, and a higher risk of asthma attacks.[112] Obesity is a known risk factor for increased hospitalizations in the pediatric intensive care unit.[113] Moreover, a clinical trial that examined the impact of obesity on treatment responses to ICS in asthmatic children found that children who were overweight or obese demonstrated a reduced response to ICS when compared to children of normal weight.[114] Several pathogenic pathways, some of which are still being fully understood, can cause obesity to impair asthma. The classical mechanism hypotheses include mechanical,[115] inflammatory, shared genetic pathways, and shared comorbidities.[116] A modified microbiome that may be linked to the severity of asthma is also related to obesity.[117] As a result, weight management and regular Body Mass Index (BMI) monitoring should be taken into account when developing asthma treatment plans for children with DA to improve asthma control.

Gastroesophageal reflux disease. Patients with severe asthma have a considerably greater prevalence of GERD than those with mild to moderate asthma. According to studies, 30–80% of asthmatic individuals suffer from GERD,[118] and asthma symptoms were aggravated by GERD.[119] Individuals with severe asthma symptoms are more likely to experience gastric reflux symptoms than those with mild or moderate symptoms. Reflux symptoms were experienced by 30%, 46%, and 70% of patients with mild, moderate, and severe asthma, respectively.[120] Another analysis found that individuals with severe asthma had a GERD prevalence of 46%, whereas those with mild to moderate asthma had a GERD prevalence of 21%.[121] Although GERD and DA are associated, its precise processes are yet unknown.[122] The effect of GERD medication on asthma

outcomes in both adults and children is still debatable. The addition of lansoprazole, a proton-pump inhibitor, as compared to a placebo, did not improve symptoms or lung function in children with poorly controlled asthma who were using ICS but was associated with an increase in adverse events. This was found in a multicenter randomized clinical trial of 306 children with poorly controlled asthma after inhaled glucocorticoid therapy.[123] Nonetheless, some academics contend that when symptomatic GERD is taken into account, children with DA should be treated appropriately.[124]

Inducible laryngeal obstruction. Inducible laryngeal obstruction (ILO), also known as VCD in the past, is marked by breathing difficulties in conjunction with severe supraglottic or glottic laryngeal constriction.[125] The most typical symptoms include coughing, stridor, tightness in the chest, and soreness in the throat. In DA sufferers, it occurs more frequently.[126] Asthma patients who have ILO/VCD account for 25–50% of all cases.[127] Patients with ILO/VCD who had asthma experienced more frequent symptoms, had higher hospitalization rates, and used more asthma medications. Yet, because it can mimic asthma symptoms and has no reaction to asthma medications, it is frequently utilized as a confounding factor in the diagnosis of asthma. Sometimes patients with ILO/VCD alone may be wrongly diagnosed as having DA.[128]

Because ILO/VCD is a dynamic and sporadic disease that may not be easily triggered during examination,[129] the prevalence of this disease in adults and children has not been fully estimated. The pediatric cohort's median age at diagnosis for ILO/VCD is 14, and nearly 80% of patients are women. ILO/VCD is more prevalent in female teenagers.[130] Notwithstanding, it must be noted that reports of ILO/VCD date back to infancy.[131]

The potential inducement of ILO/VCD is a condition that leads to an increase in throat sensitivity, such as GERD, upper respiratory tract virus infection, chemical and physical factors, etc.[104] Symptom-based assessment seems to be limited in differentiating ILO/VCD from asthma. The gold standard for diagnosing ILO/VCD is laryngoscopy, which is challenging to conduct on young patients. Indeed, individuals who have poor asthma control, aggressive attacks, or a poor response to treatment should have an ILO/VCD-related examination Symptom-based assessment seems to be limited in differentiating ILO/VCD from asthma. The gold standard for diagnosing ILO/VCD is laryngoscopy, which is challenging to conduct on young patients. Indeed, individuals who have poor asthma control, aggressive attacks, or a poor response to treatment should have a ILO/VCD-related examination.[129] Identification and effective management of ILO/VCD can significantly improve asthma consequences, lessen symptom severity, lower the risk of hospitalizations, prevent overmedication, and save medical expenses.[132]

Dysfunctional breathing. Dysfunctional breathing (DB) is characterized by recurring or persistent alterations in the respiratory rhythm that cause symptoms both inside the lungs and outside them. The most typical symptoms include dyspnea (both at rest and during exercise), chest tightness, chest pain, yawns, heavy sighs, and hyperventilation.[133] It includes respiratory pattern disturbance, hyperventilation syndrome, and malfunction of the vocal cords.[134] DB is one of the risk factors for poor symptom control and quality of life in patients with asthma.[134] According to previous research reports, surveying with the Nijmegen Questionnaire (NQ), the prevalence of DB among adult patients with DA is about 25–47%.[135]

The prevalence of respiratory dysfunction in children with asthma and its impact on asthma control were examined in a large sample ($N=203$), cross-sectional study of children. Using the NQ and the pediatric Asthma Control Questionnaire, the findings revealed that 5% of children and adolescents referred to a hospital-based pediatric asthma clinic for severe or difficult-to-control asthma had DB.[136] Despite the fact that this incidence is smaller than that of adult asthma patients, this study similarly revealed a strong dosage dependent link between dysfunctional breathing and asthma control, with dysfunctional breathing being more prevalent in kids with poor asthma control.[136] Also, another observational cohort study with 71 children with problematic asthma was addressed in a review paper. The findings showed that 15% of the participants had abnormal breathing, including hyperventilation and VCD.[137] A recent study discovered that roughly 18% of children with asthma had DB.[133] Given that the participants in the earlier trial were younger, the gap can likely be attributed to age differences.

Previous research has demonstrated that adult asthma patients who undergo breath retraining can experience clinical relief that is not possible with conventional asthma medication.[134] In children with asthma, there is limited evidence as to whether such treatment is feasible.[13] The management of asthma, quality of life, and exacerbation risk may be optimized by breathing control exercises with the assistance of a skilled physiotherapist.[24] In a cohort study of 169 children with asthma and DB, it was found that, in addition to conventional medical therapy, individually tailored physical therapy interventions, namely Buteyko Breathing methods, improved asthma control and DB in kids receiving all levels of asthma medication.[138]

Other comorbid conditions in children

Infection of Mycoplasma pneumoniae *and* Chlamydia pneumoniae. According to the available data, acute respiratory tract infections caused by atypical bacteria, such as *Chlamydia pneumoniae* or *Mycoplasma pneumoniae*, may account for 5–30% of wheezing episodes and asthma exacerbations.[139] The hypothetical mechanisms underlying the association between atypical bacteria and asthma are complex and multifactorial. It is believed that these bacteria infect the human bronchial tree, leading to ciliary dysfunction and epithelial damage. Additionally, *Mycoplasma* and *Chlamydia* can produce inflammatory cytokines both in vivo and in vitro. Moreover, *M. pneumoniae* and *C. pneumoniae*-specific IgE have been associated with asthma in both children and adults.[140]

Earlier studies on animals have demonstrated that acute *M. pneumoniae* infection enhances bronchial resistance and cytokine production, particularly in mice at risk for developing asthma.[141] Clinically, it was discovered that *M. pneumoniae* infection is frequently linked to a worsening of children's asthma in a study to identify the acute infection of *M. pneumoniae* in children with asthma.[142] Also, it has been shown that an acute *M. pneumoniae* infection may be accompanied by up to 50% of a child's first severe asthma episode.[143] *M. pneumoniae* and *C. pneumoniae* were found to significantly correlate with wheezing in children, particularly in those with a history of repeated attacks, according to Esposito *et al.*[144] A recent meta-analysis found that children with *M. pneumoniae* infections had considerably higher odds of developing asthma. And following these findings, it appears that an acute *M. pneumonia* infection might trigger asthma in children.[145]

There is mounting evidence suggesting that atypical bacterial infections can be effectively treated, which has a positive impact on the clinical symptoms of asthma. Macrolides, a type of medication with anti-inflammatory properties,[146] appear to be an useful medication for the treatment of such infections. By reducing bronchial hyperresponsiveness, macrolides appear to improve the clinical status of asthma patients. Consequently, they may be a valuable treatment option for individuals with asthma who are experiencing exacerbations due to atypical bacterial infections.[147]

Low serum vitamin D concentrations. Low serum vitamin D levels in youngsters seem to contribute to the development of asthma, a higher risk of asthma flare-ups, and a decline in lung function.[148,149] Many of these mechanisms have been described. For instance, vitamin D may affect lung growth by lowering the expression of the enzyme disintegrin metalloprotease-33, leading to a variety of asthmatic symptoms, including decreased lung function and a faster worsening of lung function as well as bronchial hyperresponsiveness.[150] This secondly, the vitamin D hormone modulates immune reactions through biological mechanisms and may have an impact on immune system development, contributing to the pathogenesis of asthma.[150] Ultimately, there are numerous methods by which vitamin D might lead to the remodeling of airway smooth muscle.[151] Several researchers have postulated a connection between the decline in vitamin D levels and the rise in asthma biomarkers (total IgE and eosinophil count).[150]

The effects of vitamin D supplementation on improving DA in children are inconclusive, despite some indications that it can delay the development of asthma in children.[24] While some studies have shown encouraging results, such as a meta-analysis that found supplementing with vitamin D significantly reduced the rate of severe exacerbations in asthmatic patients.[152] Recent research has also yielded opposing results. In a review article, it was found that there is no data to support the role of vitamin D supplementation or its hydroxylated metabolites in lowering the risk of asthma exacerbation or improving asthma control.[153]

Psychosocial factors

Compared with healthy children, children with DA may be more prone to psychosocial problems, such as anxiety, depression, inattention, hyperactivity, and opposite behaviors. Approximately 25% of children with asthma suffer from worry and/or depression.[154] A survey of children with problematic, severe asthma found that about 59% of children with poorly controlled asthma had psychosocial problems.[25] What's more, these features may be linked to poor asthma symptom control, higher usage of children's emergency medications, increased visits, and lowered life quality.[89] One-fourth of the asthma deaths found by the National Review of Asthma Mortality were related to psychosocial variables.[37] Research shows that psychological stress will aggravate the severity of the respiratory tract in children with asthma. On the contrary, respiratory tract inflammation may affect the central nervous system and aggravate the psychological stress of children through vagal and noradrenergic pathways.[155] Therefore, asthmatic children with this problem must be evaluated by a psychological expert as soon as possible and actively treated.

Treatment

Biologics

Precise treatment is an important method for treating severe asthma.[156] It is a treatment strategy that selects biologics based on the pathogenesis and corresponding biomarkers of asthma patients. This therapy usually works by acting on the immune system to regulate inflammatory reactions, thereby relieving asthma symptoms and improving lung function.

Biologics are typically used for precise treatment. Biologics can alleviate asthma symptoms and reduce lung function decline by inhibiting specific immune mediators and cells, such as IgE, IL-5, IL-4, and IL-13 receptor, and so on. This type of drug is usually made up of biological macromolecules. Common biologics for asthma include IgE-specific antibodies, IL-5 inhibitors, IL-4, and IL-13 receptor inhibitors, and so on (Figure 2). As a new asthma treatment method, the safety and efficacy of biologics have been confirmed by many clinical studies.

Anti-IgE. Omalizumab is a humanized monoclonal antibody that targets immunoglobulin E (IgE). By binding to free circulating IgE and downregulating IgE receptors on mast cells, basophils, and dendritic cells, it can reduce disease progression in allergic asthma.[157] Omalizumab is mainly used for severe refractory allergic asthma with elevated serum IgE levels ($<$1300 IU/mL) as classified in the fifth level of the Global Initiative for Asthma guidelines, and it can be administered to children over 6 years old. As a precision treatment, it has good safety and tolerability and can improve symptom control and quality of life in patients with severe refractory allergic asthma.[158] Even so, omalizumab has recently been shown to effectively enhance the clinical signs and CT pictures of nasal polyps connected to severe allergic asthma.[159] Omalizumab should be chosen for treatment of severe refractory allergic asthma with sensitization on skin prick testing or specific IgE and exacerbations in the previous year. Treatment should last for at least 4 months, and can be continued if effective. Omalizumab may have a favorable therapeutic effect, especially for children with severe refractory allergic asthma, high blood eosinophils ($\geqslant$260 μL), high FeNO ($\geqslant$20 ppb), and allergy-related symptoms.[1]

Anti-IL5/Anti-IL5R. IL-5 plays a crucial role in the growth, maturation, and differentiation of eosinophils, making it a promising therapeutic target for people with eosinophilic asthma. Blocking the IL-5 pathway can effectively inhibit the survival and maturation of eosinophils. Biological drugs such as mepolizumab, reslizumab, and benralizumab have been developed to target IL-5 and its receptor, and have shown promise in clinical trials for treating eosinophilic asthma.

Mepolizumab is a humanized IgG1/k monoclonal antibody derived from mice, which targets IL-5 to prevent its interaction with the alpha subunit of the IL-5 receptor (IL-5R).[160] It is primarily used to treat individuals with severe eosinophilic asthma who have had blood eosinophil levels $\geqslant$300 μL in the past year. Nair *et al.* and Haldar *et al.* were the first to confirm mepolizumab's effectiveness against absolutely terrible asthma. In their research, scientists discovered that this biological medication greatly prevented the deterioration of severe eosinophilic asthma symptoms while also noticeably lowering the eosinophil count in blood and sputum.[161,162] These results were also demonstrated in the follow-up phase IIb/III DREAM (Dose Ranging Efficiency and Safety with Mepolizumab) experiment.[163] Furthermore, it was discovered that mepolizumab increased the FEV1

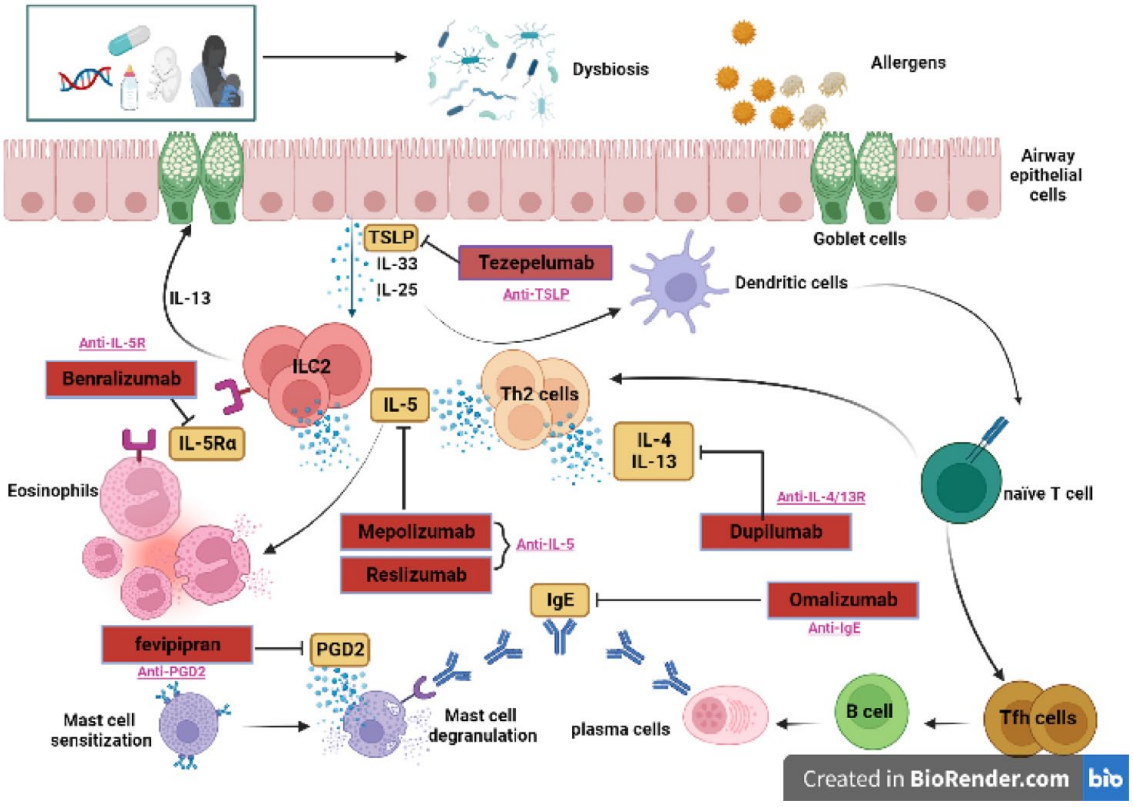

Figure 2. Biological targets for precision therapy of type 2 asthma.
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of these asthma patients in additional clinical trials for treating severe eosinophilic asthma. These studies also verified that mepolizumab decreased the percentage of asthma exacerbations, effectively controlled DA symptoms, and enhanced the general well-being of asthma patients.[164] In clinical practice, many papers have reported that mepolizumab has high effectiveness. In terms of lung function, it can lessen airflow limitation in the small airways as well as raise FEV1.[165] However, it's important to keep in mind that previous studies on the impact of mepolizumab on pulmonary function have shown some erratic results. There was no discernible difference in FEV1 between the mepolizumab-treated group and the placebo group in the research by Pavord *et al.*[163] Additionally, mepolizumab has been reported to have a beneficial therapeutic effect on severe nasal polyposis, reducing its endoscopic polyp score and alleviating its symptoms. This is advantageous for the treatment of DA patients who have nasal polyposis.[166]

Reslizumab is an intravenous agent that is a humanized IgG4/k monoclonal antibody of rat origin. Similar to mepolizumab, reslizumab also directly binds to IL-5. Reslizumab reduced the eosinophil level in blood and sputum and temporarily increased FEV_1, according to the phase II trial conducted by Kips *et al.*[167] Reslizumab significantly increased FEV_1 in a subsequent phase II study of individuals with severe eosinophilic asthma, which was associated with a non-significant tendency toward improved asthma management, particularly in asthmatic participants with high blood eosinophil counts and concurrent nasal polyposis.[168] In a number of subsequent studies, it was found that, especially for patients with severe eosinophilic asthma (eosinophils$\geqslant$400 μL or sputum eosinophils $\geqslant$3%), reslizumab can not only improve asthma control and increase FEV_1 but also lower the annual asthma deterioration rate by more than 50%. Reslizumab can improve expiratory flow and has positive effects on small airways.[158] Reslizumab use was correlated to long-term safety and tolerability, according to study data as well.

Benralizumab is a humanized, afucosylated IgG1/k monoclonal antibody of murine origin. It uniquely

binds through its Fab fragments to the α chain of the IL-5 receptor (IL-5Rα), which is expressed on eosinophils, basophils, and ILC2. This prevents the assembly of the ternary molecular complex consisting of IL-5, IL-5Rα, and the βc subunits of the IL-5 receptor,[169] thereby blocking IL-5 signal transduction. Benralizumab has a dual mechanism of action. It not only impedes all the recruitment, activation, and mobilization of eosinophils and consumes eosinophils in the circulation, bone marrow, and target tissues, particularly the airways and lungs of asthma patients, but also interacts with the surface FcγRIIIa receptor of natural killer cells through the constant Fc fraction, thus triggering eosinophil apoptosis generated by antibody-dependent cell-mediated cytotoxicity, which is arrestingly potentiated by afucosylation.[169] Numerous studies have shown that benralizumab is clinically efficacious in treating severe eosinophilic asthma as an adjuvant biological therapy. It can raise the symptom score of asthma control in such patients and improve lung function.[170]

All three of the aforementioned antibody treatments, including mepolizumab, reslizumab, and benralizumab, can lower blood eosinophil counts, reduce asthma exacerbation rates, and significantly enhance pulmonary function. They are generally applicable to children with DA who are over 12 years old. The Global Strategy for Asthma Management and Prevention (2022 update) recommends anti-IL5/anti-IL5R treatment for patients with peripheral blood eosinophil counts ⩾150 or ⩾300 μL and exacerbations of asthma in the past year, particularly for patients with DA and higher eosinophil counts, more frequent asthma exacerbations in the previous year, and those who are accompanied by nasal polyposis.[1]

Anti-IL4R. Key cytokines of type 2 T-helper cells (Th2), IL-4 and IL-13, encourage the congregation of lymphocytes, monocytes, eosinophils, and basophils. Besides, they associate with heterodimeric IL-4 receptor (IL-4R) complexes, which are crucial in the pathophysiology of allergy diseases. The IL-4/IL-13/IL-4R axis drives the adaptive immune response that speeds up allergies and activates the effector pathways in target tissues. It also supports the development of Th2 cells.[171] As a result, IL-4 and IL-13 have emerged as promising asthma biological treatment targets. A fully humanized IgG4 monoclonal antibody called dupilumab can target, bind to, and inhibit the α subunit of the IL-4 receptor, consequently inhibiting IL-4 and IL-13 signal transduction and suppressing the type 2 immune response.[172] Dupilumab is thus a dual IL-4 and IL-13 receptor antagonist. Several clinical studies have shown that dupilumab can decrease the frequency of asthma flare-ups, improve pulmonary function rapidly, and reduce the need for oral corticosteroids.[173] According to the Global Strategy for Asthma Management and Prevention (2022 update), patients with moderate-to-severe eosinophilic asthma or oral corticosteroid-dependent DA who are over 12 years old have blood eosinophils between 150 and 1500 μL, or FeNO below 25 ppb are eligible for treatment with dupilumab.[1]

Anti-TSLP. Asthma etiology is significantly influenced by the innate cytokine thymic stromal lymphopoietin (TSLP), a member of the alarmin family. TSLP is released from airway epithelial cells after tissue damage is induced by a variety of dangerous substances, including allergens, viruses, bacteria, and airborne pollutants; activating dendritic cells, mast cells, basophils, and especially group 2 innate lymphoid cells (ILC2), which contribute to the pathophysiology of T2-high asthma; and then regulating the expression of cytokines.[174] Hence, TSLP appears to be a possible ideal target for severe asthma precision therapy since it is an upstream effector of key pro-inflammatory and remodeling pathways. Tezepelumab is a completely human IgG2 monoclonal antibody targeting TSLP produced from epithelial cells. And the U.S. Food and Drug Administration has approved its use in patients with severe asthma ages ⩾12 years. It blocks TSLP from connecting with its receptor complex, suppressing Th2-mediated inflammation. In the multicenter, parallel, double-blind, randomized phase II clinical trial of tezepelumab, it was found that tezepelumab can reduce the total serum IgE concentration, blood eosinophil counts, and FeNO level; enhance the pre-bronchodilator FEV1; and lessen the annualized asthma exacerbation rate by 60–70%, independent of baseline blood eosinophil counts.[175] The most recent phase III multicenter randomized controlled clinical study, published in 2021, demonstrated that tezepelumab elevated life satisfaction, enhanced functional status, and slowed the progression of severe asthma.[176] The Global Strategy for Asthma Management and Prevention (2022 update) noted that tezepelumab is an option for treating difficult-to-control asthma exacerbations from the previous year.[1]

Anti-PGD_2. Prostaglandin D2 (PGD2), a crucial component of type 2 asthma that is mostly produced by mast cells, is another important component. Chemoattractant receptor homologous molecule expressed on TH2 cells (CRTH2), also known as D-type prostate receptor 2 (DP2), is expressed on Th2 lymphocytes, eosinophils, basophils, airway epithelial cells, ILC2 cells, and other cells.[177] PGD2 plays a pro-inflammatory role by stimulating the CRTH2 receptor, which is carried by Th2 cells, ILC2, eosinophils, basophils, and other cells.[178] Fevipiprant, a tiny molecule used as an oral medication, is a selective receptor antagonist that can prevent the binding of PGD2 and CRTH2. It is not a monoclonal antibody.[178] The results of two recent phase III randomized, double-blind, placebo-controlled, parallel-group, replicate 52-week clinical trials (LUSTER-1 and LUSTER-2) revealed that fevipiprant had no appreciable effect on lowering the exacerbation rate of asthma, despite some preliminary research results in asthmatic patients being somewhat promising.[179] Determining the fevipiprant's therapeutic potential for the treatment of asthma thus seems to be fairly difficult at this point.

Other potential therapeutic targets. GATA-binding protein-3 (GATA-3), a transcription factor that binds to and facilitates the activation of the IL-4/IL-5/IL-13 cytokine locus, is regarded as the master regulator for the differentiation and development of Th2 cells, ILC2.[180] A possible target for the therapy of asthma that is challenging to manage is GATA-3, which is also highly expressed in effector cells of different allergic inflammatory reactions. Researchers have created a GATA-3 specific DNA enzyme (GS-DNA enzyme), which can enter the cell interior (SB010), in light of the crucial role that GATA-3 plays in controlling the growth of Th2 cells and the release of cytokine.[181] SB010 is an inhaled drug based on hgd40 (a highly effective GATA-3 antagonist), which is capable of specifically binding and cleaving GATA-3 mRNA to achieve the effect of inhibiting inflammation.[182] Further clinical studies are still required to confirm SB010′s effectiveness in DA patients.

Members of the IL-17 cytokine family are mostly secreted by Th17 cells and are important controllers of neutrophil inflammation, which may be a significant factor in low-Th2 asthma. Brodalumab (AMG 827) is a human anti-IL-17RA IgG2 monoclonal antibody with high affinity for human IL-17RA, intercepting the biological activity of IL-17A, IL-17F, the IL-17A/F heterodimer, and IL-17E (IL-25).[181] A phase IIb clinical trial demonstrated that brodalumab only improved asthma patients with high FEV1 reversibility. It is not clear, though, if brodalumab would have been more effective if patients had been chosen using phenotype-specific criteria, such as the presence of prominent sputum neutropenia or the absence of obvious T2 indicators.[181]

Many research targets for severe asthma, including IL-33, ST2, IL-6, TL-1A, IL-25 (ABM125), CD6, and activated cell adhesion molecule, are in clinical trials. The therapeutic efficacy for asthma and whether it is suitable for children need to be further studied and determined.

Regulation of microbiota

Many studies have exhibited that the microbiota is a pivotal regulator of immunity, metabolism, and cell function, responds to asthma-related inflammatory signals, and may mediate asthma susceptibility, severity, and phenotype. Asthma prevalence and development are highly correlated with intestinal flora imbalance. The first 3 years of life are crucial for the process of microbial colonization, with the first 100 days of life being particularly important. Microbial dysbiosis and asthma at later ages of life have been linked, according to longitudinal cohort studies on children's gut and airway microbiomes.[183] In a different metabonomics-based investigation, the stool samples of 4 to 7-year-old asthmatic children were compared with those of healthy kids, with a focus on comparing intestinal metabolites. The findings confirmed that there was, in fact, a significant difference in the gut microbiota between asthmatic children and healthy kids. Faecalibacterium and Roseburia (phylum Firmicutes) were much less prevalent in asthmatic children, whereas Enterococcus and Clostridium (phylum Firmicutes) were more abundant.[184]

Probiotics are described by the World Health Organization as living microorganisms that, when administered in appropriate amounts to the host, will help the host's health. Its roles in the early detection and management of asthma are still not fully understood. Nonetheless, studies have illustrated that *Lactobacillus rhamnosus*

can aid in the prevention of asthma.[185] Oral probiotics may be an extra or adjunct treatment for allergic asthma, as demonstrated by multiple animal studies.[186] Clinical studies have shown that giving probiotics (*Lactobacillus acidophilus, Bifidobacterium bifidum*, and *Lactobacillus delbrueckii* subsp. Bulgaricus) orally to toddlers with allergic asthma between the ages of 4 and 10 significantly improved their pulmonary function and dropped the frequency of asthma attacks. Children with asthma aged 6–18 years were given *Lactobacillus paracasei, Lactobacillus fermentans*, or their combination for 3 months, and both the intensity of the children's symptoms and their serum IgE levels decreased.[187] Probiotics and engineered bacteria are being used to try to restore the microbiota and immunological balance. However, data from human research does not fully support their effectiveness in the clinical management of asthma.[184]

For the treatment of particular intestinal and extraintestinal disorders, fecal microbiota transplantation (FMT) involves introducing functional bacteria from healthy individuals' feces into the patients' intestines and restoring the balance of the intestinal microbiota. Although FMT may be a feasible treatment for refractory asthma, there are few reports on its effectiveness in humans. However, FMT has not yet been documented in a clinical trial for the treatment of children who are difficult to treat.

Other treatments

Azithromycin is the second generation of macrolide antibiotics. In recent years, it has been found that in addition to its basic antibacterial effects, azithromycin also has anti-inflammatory, immune regulation, antiviral, and other pharmacological functions. Azithromycin, when used as an additional treatment to standard treatment, has been shown to improve asthma control and reduce disease deterioration compared to the standard treatment group alone, according to a recent open-label randomized controlled trial for kids with poorly managed asthma.[188] However, only 120 children were included in the trial, and the sample size was small. To logically assess the safety and efficacy of azithromycin add-on medication for kids with asthma that is challenging to treat, large-scale clinical studies were required.

Bronchial thermoplasty (BT) is a prospective therapeutic approach that entails using a radiofrequency pulse to treat the airways during bronchoscopies.[189] It is suitable for patients with uncontrolled asthma who are older than 18 and can endure bronchoscopic intervention treatment without good medication management. For the time being, there are no clinical studies on the use of BT to treat childhood asthma.[189]

Conclusion

Since children have a lesser fraction of STRA than adults do, DA diagnoses in kids should be approached with caution. Once a proper diagnosis is confirmed, drug-related issues, such as children's poor compliance and ineffective equipment or inhalation technology during the maintenance phase of treatment, are frequently the most common causes contributing to poor asthma control in children. This outlines the standards for the Children's Asthma Center's physicians and nurses. When beginning treatment for children of various ages, it is important to not only write the proper prescriptions but also to educate both the child and the parent about the drug. Children's medications should be regularly examined and evaluated while they are being taken. The need to refer to an expert center with pediatric DA services arises if it is challenging to identify the modifiable variables causing poor asthma control. Only until all modifiable factors have been fully addressed and the effectiveness of the child's treatment has been regularly assessed can the diagnosis of STRA be made.

For the treatment of children with DA, there are still few medications on the market. Due to the unique characteristics of the pediatric population, many medications and treatments have not been studied in children, and results from adult studies can only be very carefully extrapolated to children. Although there is a chance to potentially address this issue with the emergence of new biological agents, the cost of this treatment is higher, and most families might not be able to bear this financial burden. Also, the use of biotherapy necessitates the clarification of the precise biological phenotype of childhood asthma, which may necessitate invasive screening of children. Consequently, finding a novel and less damaging treatment for children remains the focus of our future study.

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Not applicable.

Consent for publication
Not applicable.

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