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Review

Asthma, Infections and Immunodeficiency

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Abstract

The relationship between asthma, infections, and immunodeficiencies is complex and affects disease progression. Immune deficiencies can occur independently or because of the inflammatory processes associated with asthma. Early viral infections like respiratory sinticial virus and rhinovirus trigger asthma attacks, while bacteria such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Mycoplasma pneumoniae,* and *Chlamydia pneumoniae* worsen airway inflammation. People with asthma often have defects in innate (mucociliary clearance, interferons, defensins, NK cell, and eosinophils) and adaptive immunity such as immunoglobulin (Ig) deficiencies, making them more vulnerable to lung infections. Combined and selective deficiencies of IgA, IgG, IgM, and IgE are linked to higher asthma rates and reduced effectiveness of treatments, but immunoglobulin therapy can help control symptoms. Biologic therapies also decrease asthma exacerbations during periods of high viral activity by boosting immune responses and airway defenses. However, the link between asthma and higher infection risk is not well studied or understood, so guidelines do not recommend routinely checking for immunodeficiencies in cases of poor treatment response. More research is needed to clarify these connections and improve management strategies.

Keywords: asthma; virus; infections; immunodeficiencies; immunoglobulins

1. Introduction

Accumulating evidence supports the view that airway infections are crucial to the initiation and persistence of asthma [1-3]. Numerous studies further show that infections, especially those caused by common viruses such as rhinovirus (RV) and respiratory syncytial virus (RSV), are responsible for most asthma exacerbations in both children and adults [1-3]. The prominent role of infections in asthma pathogenesis suggests potential deficiencies in immune defense mechanisms, particularly among patients with severe asthma who show suboptimal responses to treatment [4].

The demonstrated efficacy of novel biological therapies in reducing the frequency of exacerbations in severe asthma implies that these treatments may enhance patients' immune responses to infections, thereby preventing exacerbations.

This review aims to provide an update on current knowledge about the role of infections and potential defects in host defense mechanisms among asthmatic individuals, as well as the impact of emerging biological therapies on the immune response to infections in this population.

2. Asthma: Definition and Classification

Asthma is a chronic inflammatory condition of the airways. It is typically characterized by variable and recurring respiratory symptoms, including wheezing, shortness of breath, chest

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tightness, and coughing, which are associated with reversible and variable expiratory airflow limitation and airway hyperresponsiveness [5].

Asthma includes various clinical subtypes, or phenotypes, each with potential distinct underlying mechanisms called endotypes. Phenotypes describe traits such as age of onset, gender, symptoms, and triggers. In contrast, endotypes reveal the biological causes behind these traits [6].

GINA 2025 identifies seven asthma phenotypes: Allergic Asthma, Non-allergic Asthma, Adult asthma or Late-onset Asthma, Exercise-induced Asthma, Cough-variant Asthma, Asthma with Obesity, Asthma with Fixed Airflow Obstruction [7].

Asthma has two main endotypes: T2-high and T2-low (non-T2). T2-high asthma involves eosinophils and elevated type 2 cytokines (IL-4, IL-5, IL-13) and includes allergic, eosinophilic, and aspirin-exacerbated respiratory disease phenotypes. T2-low asthma lacks T2 biomarkers and features neutrophilic or paucigranulocytic inflammation. Research studies highlight the overlap among asthma subtypes, underscoring its heterogeneity and complexity [6,8].

3. Asthma and Infections

3.1. Viral Infections

Early-life respiratory viral infections are linked to an increased risk of recurrent wheeze and asthma. Asthma onset is primarily associated with respiratory syncytial virus (RSV) and rhinovirus (especially type C) lower respiratory tract infections (LRTI) [1-3].

Research suggests that even mild cases of infant RSV infection are linked to changes in anti-viral immune function and alterations in airway cell metabolism, which may persist for years. These factors have been studied as potential mechanisms by which infant RSV infection may be related to later development of childhood asthma, including ongoing airway inflammation or changes in the airway epithelium [9].

Although causal relationship between RSV infections and asthma development has not be definitively established, there is accumulating evidence from observational studies that not having RSV infection in the first year is associated with a 26% reduced risk of developing asthma by age 5 years, with the greatest risk reduction for nonatopic asthma [10].

Additionally, a double-blind, placebo-controlled trial showed that palivizumab- a monoclonal antibody used for preventing severe RSV infections- reduced wheezing days and the rate of recurrent wheeze in preterm infants (11% vs 21%, P = .01) during their first year [11]. A follow-up study found parent-reported asthma at age 6 was lower in the RSV prevention group (14.1% vs 24.0%; absolute risk reduction 9.9%), but there were no significant differences in physician-diagnosed asthma or lung function between groups [12]. These data suggest palivizumab lowers early respiratory morbidity and parent-reported asthma, though not confirmed asthma diagnoses. While RSV vaccines and mAbs show potential for reducing disease burden, more long-term research is needed to assess lasting impacts and asthma prevention.

A recent review reports that genes involved in innate immunity and Th2 inflammation—including ADAM33, IL4R, CD14, TNF, IL13, and IL1RL1—are linked to bronchiolitis, asthma, and RSV infections, indicating a genetic predisposition for asthma patients to develop RSV infections [13].

It also is still unclear whether RV causes or merely reveals asthma, but evidence points to a possible causal link. A CDHR3 polymorphism, which raises RV-C receptor expression, increases susceptibility to RV-C infection and wheezing, and is also linked to recurrent childhood asthma [14-17].

Unlike VRS, there is currently no effective therapy available to prevent RV infections, making it challenging to evaluate its possible causal relationship with asthma.

Respiratory viruses are a leading cause of asthma flare-ups, particularly in children, with most acute cases coinciding with such infections [18]. In adults, up to 83% of asthma cases are linked to respiratory viruses [19].

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RSV is also a relevant asthma trigger, detected in 50%-80% of hospitalized cases [20]. Influenza virus also significantly contributes to severe asthma exacerbations in adults [18].

Recent studies found that children with preexisting asthma had higher exacerbation rates than controls and a greater risk of future exacerbation after COVID-19. Adults, whether hospitalized or not for COVID-19, also showed increased risk of future asthma exacerbations [21].

3.2. Bacterial Infections

Pathogenic bacteria, atypical bacteria such as Mycoplasma pneumoniae (MP) and Chlamydia pneumoniae (CP) and airway microbiota might be involved in the immunopathology of asthma [22].

3.2.1. Pathogenic Bacteria

Asthma has been identified as a significant risk factor for Streptococcus pneumoniae carriage [23] and increases the likelihood of invasive pneumococcal disease [24].

Hemophilus influenzae (HI) is a bacterium often found in the airways of asthma patients. It is linked to neutrophilic asthma and reduced corticosteroid responsiveness [25]. Its presence is linked to increased neutrophils in sputum [26]. A recent study identified a phenotype in severe asthma with high HI levels, marked by neutrophil inflammation, NETosis, and IL-6 trans-signaling [27].

Clinically, patients with abundant HI and neutrophilic inflammation may benefit from targeted antibiotics. A recent randomized trial found that 48 weeks of azithromycin in adults with uncontrolled asthma reduced HI in sputum and lowered exacerbation rates, but increased Staphylococcus aureus antibiotic resistance [28].

Moxarella catarrhalis (MC) is linked to chronic obstructive pulmonary disease and asthma exacerbations. Studies of hospitalized children with asthma found MC in nasopharyngeal swabs [29]. Additionally, children whose nasal airway microbiota are mainly colonized by MC have a higher risk of asthma exacerbation [30].

3.2.2. Atypical Bacteria

Two studies found that 38%-49% of patients hospitalized for severe asthma exacerbation showed serological markers of CP or MP infection and experienced a greater decline in lung function [31,32]. In contrast, other case–control studies did not find significant differences in the detection of CP and MP infections among adults with asthma exacerbations, those with stable asthma [33,34], or healthy controls [33]. A recent meta-analysis found that atypical pathogens were detected in 8.29% of asthma exacerbations cases, with CP accounting for 4.49% and MP for 4.24% [35].

Taken together, these data indicate that the exact etiological relationship between atypical bacteria and asthma exacerbations has yet to be fully proved.

3.2.3. Airway Microbiota

Studies show that asthmatic individuals have reduced microbial diversity and more potentially harmful bacteria like *Moraxella*, *Haemophilus*, and *Streptococcus*, while beneficial bacteria such as *Corynebacterium* and *Dolosigranulum* are often lacking. In children, upper airway microbiota dominated by *Corynebacterium* and *Dolosigranulum* is linked to better clinical outcomes than those dominated by pathogens like *Staphylococcus*, *Streptococcus*, and *Moraxella* [36-38]. Similarly, nasal bacterial profiles differ among adults with exacerbated asthma, non-exacerbated asthma, and healthy controls. Compared to controls, asthma patients showed higher levels of *Bacteroidetes* and *Proteobacteria*. Four species-*Prevotella buccalis, Dialister invisus, Gardnerella vaginalis,* and *Alkanindiges hongkongensis*—varied by asthma status and activity after adjustment for multiple comparisons [39].

Research using sputum and bronchoscopy samples reveals that patients with mild atopic asthma have a distinct airway microbiome compared to non-atopic healthy controls and atopic individuals without asthma [40]. Bacterial composition differs even among those without asthma, suggesting atopy alone is associated with altered airway microbiota, with more changes seen in asthma [41].

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Baseline bronchial bacterial burden was significantly higher in T2-low asthmatic patients than in those with a T2-high profile, suggesting that airway bacteria may have a greater influence on T2-low asthma phenotypes [40]. Mild asthma patients who hadn't used inhaled corticosteroids were randomized to receive either fluticasone propionate or a placebo for six weeks, followed by clinical reassessment and sample collection [40]. Researchers analyzed the microbiome and baseline type 2 inflammation (via IL-13 responsive genes) and measured response to fluticasone using repeat methacholine bronchoprovocation to assess improvements in airway reactivity [40]. Fluticasone treatment led to changes in airway bacterial communities not seen in the placebo group, suggesting even short-term inhaled steroids can alter the microbiome. Notably, individuals who did not respond to therapy had significantly different baseline microbial profiles and experienced greater microbial shifts after fluticasone compared to responders [40].

Airway microbiotas differ between eosinophilic (EA) and non-eosinophilic asthma (NEA). S*tenotrophomonas*, *Streptococcus*, *Achromobacter*, and *Neisseria* were consistently found in all groups. *Veillonella* was higher in NEA than in healthy controls, and *Achromobacter* was more abundant in NEA than EA, highlighting unique microbial profiles [41].

Recent research has examined how asthma severity relates to airway microbiota [42]. Analyses revealed that clinical and immunologic factors—such as sputum neutrophil counts, eosinophil levels in biopsies, bronchial gene expression, asthma control, and BMI—were linked to variations in bronchial bacteria. Increased *Proteobacteria* correlated with poor asthma control and Th17 gene markers, while *Actinobacteria* was associated with corticosteroid response. No bacterial correlation was found for type 2 gene signatures, matching the observed inverse relationship between airway eosinophils and bacterial burden; more eosinophils meant fewer bacteria. Additionally, obese individuals with severe asthma had higher levels of *Bacteroidetes* and *Firmicutes*, suggesting obesity may alter the bronchial microbiome and influence asthma outcomes [42].

A recent study found that upper airway bacterial microbiota and rhinovirus detection proved seasonal changes. Seasonal variation was seen in both baseline and respiratory illness-related microbiota, which were associated with subsequent exacerbation. During the fall—when respiratory illnesses occurred most often—certain *Moraxella* and *Haemophilus* members were more abundant in virus-positive respiratory illnesses and in those that progressed to exacerbation [43].

4. Asthma and Immunodeficiencies

Evidence indicates that asthma patients have reduced immune responses to viral and bacterial infections. This is most probably due to complex interactions between asthma-related factors, pathogen-specific immunity, altered innate and adaptive responses, comorbidities like obesity, and treatments such as inhaled corticosteroids—all of which affect lung immunity. We continue to use this classification (innate and adaptive) even though recent advances have blurred the distinction between innate and adaptive immunity.

4.1. Innate Immunity and Asthma

Innate immunity uses physical and chemical barriers, along with specialized cells and proteins, to defend the body against infections.

4.1.1. Mucociliary Clearance

When microbes reach the tracheobronchial tree, the mucociliary epithelium removes them from the lungs. Effective mucociliary clearance relies on healthy cilia and optimal mucus composition [44]. Airway mucus, a viscoelastic gel produced by goblet and mucous glands, traps inhaled particles and pathogens, aids their clearance via mucociliary action and cough [45]. Of 24 human mucine (MUC) genes, 14 are found in the respiratory tract. Airway mucins are classified as secreted monomeric, secreted gel-forming, or non-secreted surface-bound [45]. MUC5AC and MUC5B, the principal gel-

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forming mucins from goblet cells and submucosal glands, are key to mucus's viscoelastic properties [46].

The airway epithelial layer in asthma is disrupted, as indicated by detachment of ciliated cells and presence of epithelial cell aggregates in the sputum (creola bodies) affecting the ability of ciliated cells to clear mucus from the airway [47]. In patients with asthma, there is goblet cell hyperplasia, and they had higher levels of MUC5AC compared to MUC5B mucins in sputum [48]. Goblet cell hyperplasia and upregulated expression of MUC5AC might contribute to mucus accumulation and plugging, ultimately causing small airway obstruction that results in reduced capacity to eliminate pathogens [47,48].

Ciliary dysfunction and increased mucus production in individuals with asthma collectively compromise the effectiveness of mucociliary clearance mechanisms.

4.1.2. Defensins

Antimicrobial peptides (AMPs), also called host defense peptides (HDPs), are small natural antibiotics that protect against bacterial, viral, and fungal infections. In mammalian lungs, key antimicrobial molecules include defensins, cathelicidins, PLUNC proteins, lactoferrin, lysozymes, secretory leukocyte proteinase inhibitor, and surfactant proteins SP-A/SP-D [49-51].

Human defensins are classified into alpha-defensins (HAD) and beta-defensins (HBD). Alpha-defensins are predominantly produced by neutrophils and the Paneth cells of the small intestine [52]. In contrast, HBDs are mainly synthesized by epithelial cells. HBD-1 is expressed constitutively, whereas HBD-2 expression is inducible in response to bacterial contact [53].

Cathelicidins are synthesized as prepropeptides. After secretion, the procathelin domain is cleaved by serine proteases [50,51]. LL-37 is currently identified as the sole human cathelicidin, produced constitutively in several cell types, with its synthesis in immune and epithelial cells regulated by infection, tissue damage, and vitamin D3 [54].

Histatins are produced by salivary glands and are involved in defensive mechanisms within the oral cavity [55].

Natural products like calprotectin, lactoferrin, lysozyme, cathepsin, and secretory leukocyte protease inhibitor (SLPI) also help protect the airways and lung tissue from infections [49, 51, 56, 57].

The roles of various defensins have been studied in healthy individuals and those with COPD, bronchiectasis, and asthma. Research shows that SLPI and beta defensin-1 are lower in sputum from asthmatics compared to healthy subjects and COPD patients [58]. This reduction, mainly seen in severe asthma, correlates with increased IFN (Th1) immune response and greater airway hyperresponsiveness [59].

Asthmatics show significantly decreased levels of human neutrophil α-defensins (HNP1-3) and lipocalin 2 in nasal secretions [60]. HBD-2 expression is also reduced in allergic airways, correlating with Th2-driven inflammation. IL-4 and IL-13-mediated Th2 responses suppress *P. aeruginosa*-induced HBD-2 expression, delaying pathogen clearance [61].

Collectively, these observations indicate that innate immune responses reliant on defensins may be impaired in individuals with asthma, potentially diminishing their ability to combat pathogens. It remains to be determined whether the reduced production of certain defensins is independent of asthma or a consequence of the underlying inflammatory processes associated with the disease.

4.1.3. Interferons

Interferons (IFNs) are cytokines that play a key role in antiviral defense and immune regulation. There are three major types: Type I IFNs (e.g., IFN-α, IFN-β): Produced by many cell types in response to viral infections. Type II IFN (IFN-γ): Produced mainly by T cells and NK cells, crucial for immune regulation, and Type III IFNs (e.g., IFN-λ) [62].

IFNs deficiency has been implicated in the pathogenesis and severity of asthma, particularly viral-induced exacerbations. Deficiencies [63-67] or delayed [68] induction of interferons by ex vivo virus-infected bronchial epithelial cells and BAL fluid cells in asthmatic patients have been reported

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in several [64-69], but not all studies [68,69]. Interferon responses have remained challenging to define, as most studies have relied on ex vivo cultures and single-time-point sampling [62,64,68].

Mechanistic studies have more consistently shown dysregulated interferon responses [70,71]. A recent study saw IFN deficiency in the bronchial epithelium on day 4 and 6 weeks after rhinovirus infection in asthmatic patients in vivo. Lower epithelial IFN expression was related to greater viral load, worse airway symptoms, airway hyperresponsiveness, and reductions in lung function during rhinovirus infection [70]. Another study in children with exacerbation-prone asthma found that IFN gene expression increased more during colds that led to exacerbations (Ex1) than those that did not (Ex2). Higher IFN expression correlated with greater nasal viral load and lower predicted FEV1 in blood samples. Children with low baseline IFN expression had a shorter time to exacerbate, higher risk during viral illnesses, and a larger increase in IFN expression during colds. These findings suggest that variability in interferon responses influences asthma exacerbation risk in children, with low baseline IFN followed by significant upregulation during illness associated with higher risk of exacerbation [71].

These mechanistic studies may help clarify why inhaled beta-interferon therapy has not proven effective in preventing the progression of asthma symptoms when administered at the onset of cold symptoms [72]. It is likely that the therapy would be more beneficial if given prior to infection, rather than after the disease process has already begun.

It is unclear whether altered IFN regulation in asthma is a cause or effect of the disease. A recent study found that goblet and ciliated epithelial cells from asthma patients had reduced expression of interferon response genes such as *OASL*, *ICAM1*, and *TNFAIP3*, suggesting a possible genetic component to interferon deficiency [73].

4.1.4. Cells

Innate immunity uses various cells for a fast, non-specific response to pathogens. Natural killer (NK) cells attack infected cells, while phagocytes such as neutrophils, macrophages, and dendritic cells engulf and destroy invaders. Mast cells and eosinophils help defend against viruses and parasites.

Macrophages. Macrophages help defend the body by recognizing and destroying pathogens, making them crucial for innate immunity. In response to danger signals, they adapt into different forms to protect the host. However, many pathogens alter macrophage metabolism to evade immune detection and persist during chronic infections [74]. Lung macrophages help clear apoptotic cells, resolve inflammation, and contribute to airway remodeling in asthma by releasing pro-fibrotic cytokines, growth factors, and enzymes like matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) [75].

Macrophages display different phenotypes, which are altered in asthma [76]. Their role in lung defense against pathogens is still unclear. Research shows that airway macrophages from children with neutrophil-predominant severe asthma have reduced phagocytosis of *Staphylococcus aureus* compared to those with fewer neutrophils [77], and patients with non-eosinophilic asthma also show lower phagocytic capacity than those with eosinophilic asthma [78]. However, some findings differ; for example, sulfur colloid uptake by airway macrophages is higher in mild asthma than in healthy subjects [79]. Additionally, phagocytosis of *Staphylococcus aureus S.* by alveolar macrophages from children with mild-to-moderate asthma was similar across asthma types but decreased after three weeks of allergen avoidance [80]. Further study of macrophage phagocytosis and its impact on asthma-related infection is needed.

Natural Killer (NK) lymphocytes. NKs are a vital component of the innate immune system, quickly identifying and destroying infected or abnormal cells without prior sensitization. They serve as frontline defenders against viral and bacterial threats by directly killing target cells through cytolytic granules, inducing cell death pathways, and producing cytokines like IFNγ that enhance host defense. NK cells also regulate other immune responses via cytokine and chemokine secretion [81,82]. A study found that NK cells from severe asthma patients showed reduced cytotoxicity and IFN-γ

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expression compared to healthy donors after rhinovirus exposure [83]. This suggests altered NK cell function may contribute to virus-induced asthma exacerbations [84].

Neutrophils. In certain individuals with asthma there is an elevated presence of neutrophils within the airways. Proteases released by neutrophils can inflict structural damage to the airways, resulting in airway wall thickening and increased mucus secretion, both of which contribute to airway obstruction. Neutrophilic asthma is correlated with poorer clinical outcomes, including greater airway narrowing and a heightened risk of hospital admissions and emergency department visits [85,86].

However, a recent study questions the significance of high numbers of neutrophils in sputum, as neutrophilia does not differ between healthy individuals and those with asthma, nor can it distinguish between different severities of the disease. In other words, it remains unclear whether excess neutrophils play a role in the pathophysiology of asthma or are simply an incidental finding [87].

Neutrophils defend against microbes by phagocytosis, producing reactive oxygen species, releasing proteases, and forming DNA-based neutrophil extracellular traps (NETs) that trap and kill bacteria (NETosis). Efficient NETs formation is crucial for infection control, as impaired NET release raises susceptibility [88]. Although NETs trap microbes, excessive formation can harm tissues—especially lung tissue—by causing cell death. Elevated NET levels are associated with pulmonary diseases, so precise regulation is essential to prevent injury [89].

Studying neutrophil activation in asthma may be more informative than simply counting neutrophils. Evidence suggests increased NET formation in asthma, as airway biopsies from some mild asthmatics showed NETs, unlike healthy controls [90]. Asthma is also linked to reduced phagocytic activity of neutrophils after exposure to endotoxin. Following a 5 μg LPS inhalation challenge, both airway and blood neutrophils in asthmatic subjects showed decreased phagocytosis of IgG-opsonized zymosan compared to saline. This reduction correlated with higher airway neutrophil counts post-LPS exposure [91]. However, since non-asthmatic controls were not tested with LPS, it's unclear if these effects are unique to asthma.

A recent study used proteomic analysis of sputum from severe T2-high asthma patients treated with mepolizumab and identified two clusters. Cluster 1 showed persistently elevated sputum protein levels before and after treatment, as well as during exacerbations. Patients in this group had earlier onset, longer disease duration, no lung function improvement, and ongoing symptoms post-treatment. Cluster 1 also exhibited higher proinflammatory cytokines, increased epithelial alarmin secretion, greater neutrophil activation, and more frequent pathogen detection at exacerbation. Neutrophil activation—not cell count—was the main mechanism driving inflammation. No differences in T2 biomarkers were seen between clusters, indicating this reflects a pathobiological overlay rather than a distinct asthma endotype [92].

These observations indicate that neutrophil activation may play a role in severe asthma that does not respond well to standard therapies. The neutrophil-dependent pattern of inflammation could represent a potential target for therapeutic strategies, including the use of recombinant human DNase to degrade DNA, neutralization of NETs proteins with anti-histone antibodies, and the application of protease inhibitors in pulmonary diseases [93,94].

Eosinophils. Eosinophils are important in allergic diseases like asthma and play multiple roles, including defense against infections. Eosinophilic asthma that is characterized by increased sputum and/or blood eosinophil counts is driven by T2 immune responses. The eosinophilic phenotype of asthma is associated with an increased risk of exacerbation and lung function decline [95, 96]. Eosinophil accumulation and resulting T2 inflammation are primarily driven by systemic IL-5 signaling to the bone marrow, with IL-5 a key mediator of eosinophil proliferation, activation, and survival [97]. Other cytokines such as IL-13 [98] and IL-18 [99] are also involved in eosinophilia, by acting synergistically with IL-5 to promote eosinophil activation and migration. Corticosteroid therapy suppresses sputum eosinophils and reduces the rate of exacerbations.

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Ex vivo and *in vivo* studies show that murine and human eosinophils can rapidly capture various respiratory viruses and significantly reduce infectivity [100]. Eosinophils become active during viral infections, using granule proteins eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN) and nitric oxide to inactivate RNA viruses [101]. Additionally, studies have proved that eosinophil ETosis in which eosinophil lyses and releases their DNA components and intracellular proteins is involved in bacteriostatic activity against *S. aureus* and *Aspergillus fumigatus* [102, 103]. Interferons (IFN-α and IFN-γ) lead human eosinophils to increase the production of antiviral molecules. In addition, IFN-γ elevates the expression levels of the IL-5 receptor (IL5RA), ICAM-1, and the IgG receptor (FCGR1A), which may affect cellular responses to IL-5, promote ICAM-1-mediated adhesion to rhinoviruses, and influence IgG-triggered inflammatory reactions [104].

Studies show that eosinophils from asthma patients, especially those with severe asthma, have reduced antiviral activity compared to healthy individuals [100]. These eosinophils from severe asthma also suppress IFN-α production in airway epithelial cells and impair plasmacytoid dendritic cell (pDC) function, which may worsen asthma during viral infections [105]. Eosinophilic airway inflammation in moderate-to-severe asthma is associated with reduced TLR7 expression, resulting in an impaired antiviral IFN response [106].

Epithelial cells. Following RV exposure, epithelial cells release type I and III IFNs, a response defective in the epithelial cells of patients with asthma [66,107,108].

Mast cells. Mast cells play a central role in allergic reactions by releasing histamine, cytokines, and other inflammatory mediators when allergens cross-link immunoglobulin E (IgE) bound to their surface receptors. Two main types of human mast cells exist: MC T (tryptase only) and MC TC (tryptase and chymase). Beyond allergy, mast cells aid in defending against parasites, bacteria, viruses, and fungi by increasing their numbers during infection, storing antimicrobial peptides like cathelicidin, and killing pathogens such as *Staphylococcus aureus* and *Escherichia coli*. They can also trap and phagocytose a range of microbes. Additionally, mast cells link innate and adaptive immunity by influencing dendritic cells, B cells, and T cells [109]. IL-4 enhances interferon production by human mast cells in response to RSV and reovirus infections [110], while IL-5 treatment increases type I and III interferon levels and protects mast cells from apoptosis-induced stress compared to untreated controls [111].

Although mast cells are known to play important roles in asthma, their role in defense of infections for these patients remains unclear.

4.2. Adaptive Immunity and Asthma

The adaptive immune response follows activation of the innate system and targets pathogens more precisely through humoral and cell-mediated immunity. B lymphocytes produce pathogen-specific antibodies (humoral immunity), and T lymphocytes eliminate infected cells while boosting immune responses (cell-mediated immunity). Disruption in B-cell development causes antibody-deficiency disorders, while T-cell defects can lead to cellular and combined immunodeficiencies due to their role in supporting B-cell function [112].

4.2.1. Inborn Errors of IMMUNITY (IEIS)

IEIS, previously known as primary immunodeficiencies, are genetic conditions that impair the immune system and lead to higher risks of infection, autoimmunity, autoinflammation, bone marrow failure, or malignancy [113].

A recent report divides IEIs into 10 main categories, with further grouping by overlapping phenotypes. Antibody deficiencies include conditions like common variable immunodeficiency (CVID), with or without known gene associations such as APDS, CD19, CD20, CD21, CD81, TACI, BAFF receptor, TWEAK, IKAROS, and CIN85. Other immunoglobulin (Ig) deficiencies—such as isolated IgG subclass deficiency, selective IgA or IgM deficiency, and specific antibody deficiency are also listed [114]. Although not formally recognized, selective IgE deficiency has been suggested by recent studies and considered in this review [115-118].

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Because immunoglobulin-deficient responses are the IEI most often linked to asthma and may offer therapeutic benefits, this review will focus on these processes.

4.2.2. Immunoglobulins

Immunoglobulins, or antibodies, are glycoproteins made by plasma cells. B cells respond to immunogens, such as bacterial proteins, by differentiating into plasma cells that produce antibodies for humoral immunity against various pathogens and antigens. Antigens bind to B-cell receptors, triggering antibody synthesis specific to the stimulating antigen. Each B cell clone produces a unique immunoglobulin, and memory B cells ensure rapid responses upon re-exposure to the same antigen. Circulating antibodies recognize antigens in body fluids and serum. There are five types of immunoglobulins in humans: IgM, IgG, IgA, IgE and IgD [119].

Immunoglobulins consist of two light and two heavy chains, arranged in a light-heavy-heavy-light structure. The heavy chains vary among classes and have an Fc region for biological functions (like binding to cell receptors) and Fab regions with antigen-binding sites. Chains are organized into domains: heavy chains have 4–5 domains, light chains have two. The three hypervariable regions in each V domain of both chains form two antigen-binding sites per monomer. Antibodies perform multiple roles, including complement activation, opsonization, microbial attachment prevention, and neutralization of toxins and viruses [120].

4.2.3. Immunoglobulin Deficiencies and Asthma

Immunoglobulin deficiencies are conditions where serum Igs levels are abnormal or immune responses are insufficient despite normal Igs levels.

Common variable immunodeficiency (CVID) and asthma. CVID is a primary humoral immunodeficiency marked by low IgG, IgA, or IgM levels and frequent sinopulmonary infections, autoimmune issues, granulomatous disease, increased cancer risk, and poor antibody responses. As the most common symptomatic primary immunodeficiency worldwide, CVID encompasses diverse hypogammaglobulinemia syndromes caused by various genetic defects. "Variable" describes its wide range of clinical presentations [128]. Common variable immunodeficiency (CVID) is diagnosed when no monogenic cause is found; if a specific mutation is detected in patients with CVID-like symptoms, they are reclassified as having a CVID-like disorder due to that mutation [121].

Reported rates of asthma diagnosis in CVID patients differ considerably; some studies do not include asthma [122, 123], while others report rates between 22.2% and 42.1% [124-127]. This disparity is due to diverse patient presentations under CVID umbrella, influenced by IgG and IgA deficiencies, the latter being linked to higher rates of atopy and asthma [128]. Asthma is often diagnosed clinically based on symptoms like cough, dyspnea, and wheezing, which may also occur in other airway diseases such as COPD or bronchiectasis [127,129]. Therefore, it is important to consider alternative causes of obstructive lung disease in CVID, as some cases may be misdiagnosed as asthma. The application of diagnostic tests, such as assessments for bronchial hyperresponsiveness, tends to lead to a reduced rate of asthma diagnoses based on clinical manifestations [127, 130].

Recent reports show that CVID can affect asthma patients who do not respond to standard treatments, including biologics [131-133]. Diagnosing CVID and starting gammaglobulin therapy led to significant improvements in symptoms, fewer infection-related flare-ups, and better lung function [131-134].

Selective IgG deficiency and asthma (SIgGD). Research indicates that CVID and sIgGD have distinct disease profiles; CVID is associated with immune dysregulation and greater immune impairment. Asthma has not been seen among the diseases affecting individuals with sIgGD [123].

IgG subclass deficiency (IGGSD) *and asthma*. IgG subclass deficiency (IgGSD) is characterized by frequent or severe upper or lower respiratory tract infection, one or more subnormal IgG subclass level(s) unexplained by other causes, and decreased IgG response to pneumococcal polysaccharide vaccination. IgG1 accounts for approximately two-thirds of total IgG; therefore, individuals deficient

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in this subclass often have low total IgG and may also be classified as having IgG deficiency. The most often observed isolated IgG subclass deficiencies are IgG2 or IgG3 [135].

Studies examining the relationship between IgG subclass deficiencies and asthma present differing results. Asthma was diagnosed in 18% of patients with subnormal IgG1 and 28.3% of those with both IgG1 and IgG3 deficiencies [135]. Reduced IgG1 levels were noted in 22% of patients with brittle asthma and 18.2% with infective asthma exacerbations, but not by those with well-controlled asthma [136]. "Brittle Asthma" refers to unpredictable, severe attacks linked to fluctuating peak expiratory flow [137]. Another study found 23.5% of subjects with selective IgG3 deficiency had asthma [138].

Several open-label studies have found that gammaglobulin replacement therapy is associated with clinical outcomes such as improvement in infection-related asthma exacerbation, asthma control, and quality of life [138-140]. Additionally, in patients with non-T2 asthma, the therapy appears to increase Th2 markers like blood eosinophils, which suggests that gammaglobulin therapy may influence asthma phenotype [139].

Specific antibody deficiency (SAD*) and asthma.* SAD is a primary immunodeficiency disease characterized by normal IgA, IgM, total IgG, and IgG subclass levels, but with recurrent infection and diminished antibody responses to polysaccharide antigens following vaccination. However, there is a lack of consensus about the diagnosis and treatment of SAD, and its clinical significance is a matter of debate [141].

A multicenter observational study of 55 adult patients with SAD found that 21 individuals (38%) had a history of allergic or inflammatory conditions, primarily asthma (21.8%) [142]. SAD has been categorized into four subtypes—severe, moderate, mild, and memory—according to the degree of non-responsiveness to polysaccharide vaccines [143]. In a recent retrospective analysis of 595 patients with chronic rhinosinusitis (CRS) assessed for humoral immunodeficiency, SAD emerged as the most prevalent immune deficiency (24.2%), followed by CVID (5.9%). Severity stratification of SAD in these patients classified 45% as mild, 40% as moderate, and 15% as severe. Among the 136 CRS patients with asthma, the severity of asthma was also evaluated. Results indicated that patients diagnosed with moderate or severe SAD were more likely to exhibit moderate to severe asthma compared to those with mild SAD, according to established guidelines [144].

A retrospective analysis of 20 patients with difficult-to-treat asthma and laboratory-confirmed SAD found that intravenous immunoglobulin replacement therapy was associated with reduced morbidity, fewer hospitalizations, less steroid use, and fewer respiratory infections [145].

Selective IgA deficiency (SIgAD) and asthma.

SIgAD is the most common inborn error of immunity (IEI), with prevalence rates among blood donors ranging from 1:163 in Spain and 1:143 in the Arabian Peninsula to 1:4100 in China and 1:18,550 in Japan [146, 147]. A study conducted by the World Allergy Organization (WAO) indicated that SIgAD is the second most prevalent primary immunodeficiency (PID) associated with allergies [148]. In addition to low serum IgA, SigAD patients have reduced secretory IgA, making them susceptible to recurrent bacterial infections. The lack of mucosal IgA also increases exposure to aeroallergens and food antigens, which may promote allergies [149].

According to a recent meta-analysis, the pooled prevalence rates for asthma, allergic rhinitis, and allergic conjunctivitis in patients with SIgAD were 19.06%, 15.46%, and 11.68%, respectively [150]. In another more recent study not included in the previously mentioned meta-analysis, respiratory allergies—particularly rhinitis—were reported in 97.8% of patients, with asthma occurring in 67% [151]. Additionally, SIgAD was identified in 3.8% of individuals with severe asthma [152].

Selective IGM deficiency (SIgMD) and asthma. SIgMD is marked by low or absent IgM levels. Some individuals show no symptoms, while others experience issues like chronic sinusitis, respiratory infections, or pneumonia [153, 154]. Studies report SIgMD prevalence in healthy people between 0.03% and 0.37% [155, 156].

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About one-third of people with SIgMD have autoimmune diseases and 30–45% experience asthma or allergic rhinitis [157-161].

There is currently no definitive data on the optimal therapeutic management of SIgMD. Immunoglobulin therapy may be considered for patients experiencing recurrent or severe infections [162]. The impact of this therapy on asthma has not been set up.

Selective IgE deficiency (SIgED) and asthma. IgE is present in the lowest concentration in serum among Igs and has a shorter half-life compared to IgG (approximately 2 days versus 21 days). It circulates in the bloodstream and attaches to cells by interacting with its receptors, FcεRI and CD23. The high-affinity receptor, FcεRI, is primarily expressed on mast cells and basophils. When bound to FcεRI, IgE can remain for several weeks to months. Crosslinking of IgE attached to FcεRI leads to aggregation of these receptors, which triggers the release of preformed mediators from mast cells and basophils, resulting in immediate hypersensitivity reactions [163].

A systematic review of seven adult studies indicates that healthy individuals typically exhibit lower reference limits for IgE ranging from 0.7 to 5.7 kU/L [164]. Decreased serum IgE levels are frequently observed in conjunction with other immunoglobulin deficiencies; therefore, additional diagnostic evaluation is advised when low IgE concentrations are found [165]. Most of the research defines low IgE as values below 2.5 IU/mL, which is the lowest detection limit achievable using standard laboratory methodologies.

Selective IgE deficiency has not been recognized or included among the immunoglobulin deficiencies listed in IEIS. Nevertheless, both earlier [166,167] and more recent studies have demonstrated that isolated low levels of IgE are associated with autoimmune and autoinflammatory conditions, allergies, increased susceptibility to infections, and malignancym[115, 116,118,168-174]. Patients with sIgED respond less to polysaccharide vaccines than healthy controls, indicating an immunodeficiency that may raise infection risk [175].

SIgED has also been linked to a higher prevalence of non-allergic reactive airway diseases—including rhinorrhea, nasal congestion, dry cough, and/or wheezing (73% compared with controls) [166]—as well as asthma or hyperreactive airway disease in children 26.5% vs. 6.8% in controls [167]. Other research has reported varying prevalences of asthma, ranging from 3.59% to 38.9% [170], which underscores the limitations inherent in these retrospective studies and highlights multiple sources of bias, including the methods employed to set up an asthma diagnosis. More prospective studies involving broader populations are required to clarify the role of SIgED in the development of pathologies commonly linked to immunodeficiencies. Such research may determine whether SIgED should be classified among current antibody deficiencies.

5. Asthma, Infections, Immunity and Therapies

Respiratory viruses significantly contribute to asthma development and exacerbations, while bacterial infections can also cause ongoing airway inflammation and can contribute to attacks [1-3, 9-12, 22-23, 31-34]. Multiple deficiencies in the innate and adaptive immune systems increase the susceptibility of individuals with asthma to more frequent and persistent lung infections compared to those without asthma [64-68,72,74,77-79,81,84,101,109]. Since infections are highly relevant to asthma, effective treatment should target immune deficiencies to lower the rate and intensity of exacerbations caused by pathogens.

Potential mechanisms underlying the efficacy of antiasthmatic agents—including corticosteroids, antibiotics such as azithromycin, and emerging biological therapies—are as follows: 1. Reduction of inflammation and restoration of airway epithelial integrity enhances nonspecific innate defences, such as mucociliary clearance, defensin production, and macrophage activity. 2. Augmentation of specific antiviral defence mechanisms, particularly through increased interferon activity. 3. Enhancement of adaptive immune responses by modulating dendritic cell function, lymphocyte activity, and immunoglobulin production.

Research indicates that low-dose inhaled corticosteroids (ICS) are associated with reductions in exacerbations and asthma-related mortality rates [176,177]. When a long-acting β2-agonist (LABA) is

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added to ICS, there is further decrease in the frequency, severity, and duration of exacerbations [178]. Since viruses are estimated to be responsible for 50%-70% of all exacerbations, it is plausible that the incidence of virus-induced exacerbations could also be reduced [179,180].

Maintenance ICS lowered RV (especially RV-C) detection rates in school-age asthma inpatients, while CS treatment had no effect on overall viral detection. This suggests ICS may specifically suppress RV-C-induced immune responses, helping to prevent exacerbations [181].

The mechanisms through which corticosteroid therapy mitigates or prevents virus-induced asthma exacerbations are diverse. In vitro research has demonstrated that corticosteroids inhibit cytokine release induced by rhinovirus and respiratory syncytial virus (RSV) [180-184]. In allergic individuals a T2-skewed immune environment—marked by elevated IL-4, IL-5, and IL-13—can suppress IFNs production, impair the function of dendritic cells and NK cells, and compromise epithelial barrier integrity, thereby diminishing the innate antiviral and antibacterial host defense response [62, 184, 185]. Furthermore, exposure to T2 cytokines may attenuate antiviral interferon responses in respiratory epithelial cells following viral exposure [186]. Corticosteroid treatment is known to suppress both allergic and non-allergic type 2 inflammation [187] and enhance the antiviral activity of eosinophils [188]. Overall, these findings indicate that several mechanisms participate in the effectiveness of corticosteroids in reducing virus-induced asthma exacerbations.

Long-term, low-dose azithromycin as an adjunct therapy has been shown to reduce asthma exacerbations and improve quality of life in adults with persistent, uncontrolled asthma, including those with severe forms and both eosinophilic and non-eosinophilic phenotypes [189, 190]. In individuals with severe asthma who continue to experience exacerbations despite biologic therapy, the addition of azithromycin was associated with a significant decrease in both steroid- and antibiotic-requiring events, as well as notable improvements in asthma control [191,192].

The anti-asthmatic effects of azithromycin are not fully understood, but may include antibacterial actions [191], antiviral activity through enhanced IFNs release [192, 193] and reduced virus replication [194], as well as immunomodulation by lowering proinflammatory cytokines such as TNF [195] and IL-5 [196]. Macrolide resistance was seen to increase with prolonged, low-dose azithromycin therapy and should be taken into account during decision-making processes [191].

Biological therapies for asthma include omalizumab (IgE), mepolizumab and reslizumab (IL-5), benralizumab (IL-5 receptor), dupilumab (IL-4/IL-13 receptor), and tezepelumab (TSLP).

Omalizumab is a monoclonal antibody that binds to free IgE in the bloodstream, preventing its interaction with mast cells and reducing allergic responses. This action helps control allergic asthma symptoms, decreases asthma attacks, and lowers the need for corticosteroids and emergency care [197, 198]. Additionally, omalizumb has been shown to reduce tissue eosinophilia [199]. Importantly omalizumab reduces the peak of seasonal exacerbations caused by viral infections in both children and adults [200-204].

Omalizumab's antiviral effects are, at least in part, linked to its ability to enhance virus-induced IFN-α responses from peripheral blood mononuclear cells in children with exacerbation-prone asthma. [205]. Increased IFN-α production correlates with lower asthma exacerbation rates and reduced FcεRIα expression in pDCs, especially when IgE is cross-linked [201,205]. These results support the finding that allergic sensitization contributes to increasing susceptibility to virus-induced asthma exacerbations [206].

Mepolizumab and reslizumab are humanized monoclonal antibody against interleukin-5, a cytokine involved in the development, recruitment and activation of eosinophils. Both anti-IL-5 are indicated in the treatment for severe eosinophilic asthma, and significantly improve asthma control, reduce exacerbation rates, enabling reduction of oral corticosteroids, and improve quality of life in patients with high baseline blood eosinophil counts [207, 208]. These biologics with anti-eosinophilic significantly reduce asthma exacerbations in patients with severe asthma [209-214].

While lower eosinophil levels could theoretically increase viral infections and asthma attacks, anti-eosinophilic biologics have not shown this effect. Anti-IL-5 treatments such as mepolizumab lower asthma exacerbations during autumn, when respiratory viruses are prevalent, in both children

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and adults [212,214]. A direct antiviral effect of anti-IL-5 remains possible, as lowering eosinophil levels has been associated with increased IFN-α release in experimental models indicating that IL-5 inhibition may have antiviral effects [215]. Additionally, mepolizumab enhanced circulating natural killer cells and secretory IgA production [216]. Finally, reduced eosinophil inflammation may result in less airway inflammation and stronger epithelial defenses [217].

Benralizumab is a humanized antibody that targets and inhibits extracellular IL-5Rα, thereby blocking IL-5 signaling. It also interacts with FcRγIIIa on natural killer cells and macrophages, easing the apoptosis of eosinophils and basophils through antibody-dependent cell-mediated cytotoxicity [218].

Benralizumab significantly reduced asthma exacerbations in all seasons for patients with severe eosinophilic asthma compared to placebo, suggesting that lowering eosinophilic inflammation decreases exacerbations, even during periods of frequent virus-induced attacks [219-221]. Like mepolizumab, benralizumab also boosted rhinovirus-induced IFN-α secretion, transcription, and basal IFN-stimulated gene expression in isolated pDCs [215].

Collectively, these observations indicate that reduced eosinophil numbers or even eosinophil depletion do not adversely affect antiviral defense mechanisms in severe eosinophilic asthma.

Dupilumab targets the alpha subunit of the IL-4 receptor, inhibiting both IL-4 and IL-13 signalling, which reduces T2 inflammation [222]. Studies have shown that treatment with dupilumab is associated with long-term efficacy in reducing asthma exacerbations and decreased respiratory infections throughout all seasons compared to placebo [223-225]. Dupilumab-mediated reduction of T2 inflammation may contribute to lower rates of virus-induced exacerbations [225]. Additionally, reduced T2 inflammation could improve epithelial barrier function. Evidence indicates that du6ilumab can help restore cilia function in both healthy individuals and those with asthma [227]. Dupilumab treatment has been linked to an increase in serum club cell secretory protein 16 (CC16), along with improvements in asthma symptoms, quality-of-life scores, FEV1, and frequency of exacerbations [227]. CC16 is produced by club cells in the airways and functions as both an anti-inflammatory and protective mediator [228].

Tezepelumab is a biological therapy for severe, uncontrolled asthma that works by blocking the TSLP receptor [229]. It has shown significant reductions in asthma exacerbations and improvements in lung function and quality of life in uncontrolled severe asthma versus placebo including eosinophilic and non-eosinophilic asthma [230-233]. Tezepelumab treatment results in reductions of asthma exacerbations during each calendar season compared to placebo [233]. Like other biologics, tezepelumab may prevent viral-induced asthma exacerbations through multiple mechanisms. Research indicates that tezepelumab blocks TSLP, reducing airway inflammation such as IL-33 and T2 cytokines in asthma patients exposed to viruses, while preserving antiviral immunity [234]. Viral infections decrease IgA antibody production by epithelial cells—key for neutralising viruses at mucosal surfaces—a reduction that tezepelumab can prevent [235].

Taken together, these results suggest tezepelumab helps stabilize the bronchial immune response to respiratory viruses by targeting TSLP.

In summary, studies indicate a significant reduction in asthma exacerbations with the use of biological therapies, even during periods of increased respiratory viral activity. These therapies lower susceptibility to respiratory virus infections through complex mechanisms, including inhibition of the T2 inflammatory pathway [200,215,222,234], enhancement of airway barrier defense functions [227,228], augmentation of virus-induced interferon (IFN) responses [201,205,215,234] and enhancing NK circulating cells and increase in IgA secretion [216, 235],

6. Discusion

Infections caused by viruses and other pathogens are recognized as factors in both the development and worsening of asthma [1-3, 9-13]. Patients with either innate or adaptive immune deficiencies may be more susceptible to these infections Such immune deficiencies can occur independently or as a result of the inflammatory processes associated with asthma [61,62,64-

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68,72,78,79,84,93,101,106,108,109,115-118,124-128,130,131 144, 152,159,160, 167, 168,171]. Individuals with severe or poorly controlled symptoms may have an underlying immunodeficiency, including possible deficiencies in certain immunoglobulin classes, which could contribute to limited responses to antiasthma therapies, such as biologic treatments Immunoglobulin administration has shown to effectively improve asthma control in patients with asthma associated to diverse subtype of immunoglobulin deficiencies [131-133,135,137-139,144,161]. Additionally, asthma phenotype can be modulated by respiratory infections in immudeficient patients and treatment with immunoglobulin [93, 138]

Few studies have systematically explored immunodeficiencies in asthma. In one, 5.49% of 2,866 asthma patients had primary immunodeficiencies, mostly IgG3 subclass deficiency (58%), which raised their risk of exacerbation by 1.6 times. Among those with IGGSCD, 23.3% also had SAD, though some had only IGGSCD [236].

A recent study found that individuals with both asthma and primary immunodeficiencies tend to experience more severe conditions and more frequent exacerbations [237].

Despite all these observations, the potential mechanisms involved in the increased susceptibility to infection has been rarely be investigated or diagnosed in studies performed in the whole asthma population or in the severe asthma subgroup.

A review of numerous cohort studies on asthma shows that assessment of immunodeficiencies for determining the pheno/endotype or to partially explain asthma severity is not included among the comorbidities considered to influence asthma classification and therapeutic response [238-242].

A U-BIOPRED study reported that severe asthma patients who do not respond to high-dose ICS frequently exhibit characteristics such as rhinosinusitis, nasal polyps, obesity, underweight status, sleep apnoea, a history of reflux, vocal cord dysfunction, cardiovascular disease, eczema, and atopy. These findings indicate areas where asthma control may be addressed. Immunodeficiencies were not evaluated in this cohort [242].

A SARP study found respiratory viruses in 24% of asthma sputum samples, with high viral presence linked to a 14-fold higher risk of T1-high disease. Corticosteroid-associated improvements in FEV_1 occurred only in patients with T1-low/T2-high disease and not in patients with T1-high/T2-high disease [243]. Another study from the same cohort found that the history of pneumonia was a stronger risk factor for severe asthma. The authors indicate that this finding calls for further research into possible changes in innate immune mechanisms shared by both conditions [244].

However, further research on immune mechanisms has not been systematically conducted in these large patient cohorts with varying severity. The lack of data explains why immune deficiencies are not typically listed among comorbidities in the latest asthma guidelines for patients who respond poorly to treatment [7].

7. Conclusions

Evidence suggests that asthma may be associated with primary immunodeficiencies, which can increase susceptibility to infections and potentially affect asthma symptoms and severity. Despite their possible influence on the development and progression of the disease, there is limited information on the prevalence, clinical relevance, and therapeutic options for various immunodeficiencies.

Serum immunoglobulin level measurement is commonly used when an immune deficiency is suspected; however, it is not typically recommended by asthma guidelines for patients with severe asthma or frequent respiratory infections. Early identification is important for implementing effective treatment strategies that may improve asthma management and prevent further progression. Many individuals with immunodeficiencies remain undiagnosed.

Therapies such as azithromycin and immunoglobulin replacement have shown effectiveness in improving asthma control, decreasing infection-related exacerbations, and enhancing quality of life in patients who do not respond well to standard asthma treatments.

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Given the significance of immunodeficiencies in asthma and the potential influence of their treatment on disease progression, it is essential to conduct research that can broaden our limited understanding of this topic. Such studies may enhance our knowledge of the onset and development of asthma and contribute to improved management, especially for patients with severe forms of the disease.

References

1. Hartert T, Kvysgaard JN, Thaver L, Suara-Istanbouli A, Allinson JP, Zar HJ. Understanding the childhood origins of asthma and chronic obstructive pulmonary disease: Insights from birth cohorts and studies across the lifespan. J Allergy Clin Immunol. 2025; 155:1703-1719.
2. Zar HJ, Cacho F, Kootbodien T, Mejias A, Ortiz JR, Stein RT, et al. Early-life respiratory syncytial virus disease and long-term respiratory health. Lancet Respir Med. 2024; 12:810-821.
3. Melén E, Zar HJ, Siroux V, Shaw D, Saglani S, Koppelman GH, et al. Asthma Inception: epidemiologic risk factors and natural history across the life course. Am J Respir Crit Care Med. 2024; 210:737-754.
4. Christou EAA, Giardino G, Stefanaki E, Ladomenou F. Asthma: An Undermined State of Immunodeficiency. Int Rev Immunol. 2019; 38:70-78.
5. Porsbjerg C, Melén E, Lehtimäki L, Shaw D. Asthma. Lancet. 2023; 401:858-873.
6. Fuhlbrigge AL, Sharma S. Unraveling the heterogeneity of asthma: Decoding subtypes of asthma. J Allergy Clin Immunol. 2025; 156:41-50.
7. GINA guidelines, available from: www.ginasthma.org
8. Grunwell JR, Fitzpatrick AM. Asthma phenotypes and biomarkers. Respir Care. 2025; 70:649-674.
9. Makrinioti H, Hasegawa K, Lakoumentas J, Xepapadaki P, Tsolia M, Castro-Rodriguez JA, et al. The role of respiratory syncytial virus- and rhinovirus-induced bronchiolitis in recurrent wheeze and asthma: a systematic review and meta-analysis. Pediatr Allergy Immunol 2022;33: 13741.
10. Rosas-Salazar C, Hartert TV. Infant respiratory syncytial virus infection and childhood asthma: A shift in the paradigm? Clin Transl Med. 2023; 13:1414.
11. Rosas-Salazar C, Chirkova T, Gebretsadik T, Chappell JD, Peebles RS Jr, Dupont WD, et al. Respiratory syncytial virus infection during infancy and asthma during childhood in the USA (INSPIRE): a population-based, prospective birth cohort study. Lancet. 2023; 401:1669–1680.
12. Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra PL, Meijer A, Kimpen J, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. N Engl J Med. 2013; 368:1791–1799.
13. Larkin EK, Hartert TV. Genes associated with RSV lower respiratory tract infection and asthma: the application of genetic epidemiological methods to understand causality. Future Virol 2015; 10:883–897
14. Scheltema NM, Nibbelke EE, Pouw J, Blanken MO, Rovers MM, Naaktgeboren CA, et al. Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomized controlled trial. Lancet Respir Med. 2018; 6:257–264
15. Bonnelykke K, Coleman AT, Evans MD, Thorsen J, Waage J, Vissing NH, et al. Cadherin-related family member 3 genetics and rhinovirus C respiratory illnesses. Am J Respir Crit Care Med. 2018; 197:589–594.
16. Basnet S, Bochkov Y, Brockman-Schneider R, Kuipers I, Aesif SW, Jackson DJ, et al. CDHR3 asthma-risk genotype affects susceptibility of airway epithelium to rhinovirus C infections. Am J Resp Cell Mol Biol. 2019; 61:450–458.
17. Bonnelykke K, Sleiman P, Nielsen K, Kreiner-Moller E, Mercader JM, Belgrave D, et al. A genome-wide association study identifies CDHR3 as a susceptibility locus for early childhood asthma with severe exacerbations. Nat Genet. 2014; 46:51–55.
18. Johnston SL, Pattemore PK, Sanderson G, Smith, S., Campbell MJ, Josephs LK, et al. The relationship between upper respiratory infections and hospital admissions for asthma: A time-trend analysis. Am. J. Respir. Crit. Care Med. 1996;154: 654–660.
19. Papadopoulos NG, Christodoulou I, Rohde G, Agache I, Almqvist C, Bruno A, et al. Viruses and bacteria in acute asthma exacerbations–a GA² Len-dare systematic review. Allergy. 2011:66: 458–468.
20. Jartti T, Bønnelykke K, Elenius V, Feleszko W. Role of viruses in asthma. Semin. Immunopathol. 2020; 42:61–74.

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21. Duong KE, Henry SS, Cabana MD, Duong TQ. Longer-Term Effects of SARS-CoV-2 Infection on Asthma Exacerbation. J Allergy Clin Immunol Pract. 2025: 2213-2198(25)00434-9. A head of print.
22. Guilbert TW, Denlinger LC. Role of infection in the development and exacerbation of asthma. Expert Rev Respir Med. 2010; 4:71-83.
23. Jounio U, Juvonen R, Bloigu A, Silvennoinen-Kassinen S, Kaijalainen T, Kauma H, et al. Pneumococcal carriage is more common in asthmatic than in non-asthmatic young men. Clin Respir J. 2010; 4:222-9.
24. Talbot TR, Hartert TV, Mitchel E, Halasa NB, Arbogast PG, Poehling KA, et al. Asthma as a risk factor for invasive pneumococcal disease. N Engl J Med. 2005; 352:2082-90.
25. Zhang J, Zhu Z, Zuo X, Pan H, Gu Y, Yuan Y, et al. The role of NTHi colonization and infection in the pathogenesis of neutrophilic asthma. Respir Res. 2020; 21:1-12.
26. Simpson JL, Daly J, Baines KJ, Yang IA, Upham JW, Reynolds PN, et al. Airway dysbiosis: Haemophilus influenza and Tropheryma in poorly controlled asthma. Eur Respir J. 2016; 47:792-800.
27. Versi A, Azim A, Ivan FX, Abdel-Aziz MI, Bates S, Riley J, et al, U-BIOPRED study group. A severe asthma phenotype of excessive airway Haemophilus influenzae relative abundance associated with sputum neutrophilia. Clin Transl Med. 2024; 14:70007.
28. Taylor SL, Leong LEX, Mobegi FM, Choo JM, Wesselingh S, Yang IA, et al. Long-term azithromycin reduces Haemophilus influenzae and increases antibiotic resistance in severe asthma. Am J Respir Crit Care Med. 2019; 200:309.
29. Romero-Espinoza JA, Moreno-Valencia Y, Coronel-Tellez RH, Castillejos-Lopez M, Hernandez A, Dominguez A, et al. Virome and bacteriome characterization of children with pneumonia and asthma in Mexico City during winter seasons 2014 and 2015. PLoS One 2018; 13:1-14.
30. McCauley K, Durack J, Valladares R, Fadrosh DW, Lin DL, Calatroni A, et al. Distinct nasal airway bacterial microbiotas differentially relate to exacerbation in pediatric patients with asthma. J Allergy Clin Immunol. 2019; 144:1187-1197.
31. Kubota Y, Nakajima M, Niki Y, Kawane H, Matsushima T. Chlamydia pneumoniae and exacerbations of asthma in adults. Ann Allergy Asthma Immunol. 1998; 80:405-409.
32. Zhou A,1998; 80:40555n X, Chen Z, Shen H. Correlations of Mycoplasma pneumonia infection with airway inflammation and asthma control in patients with bronchial asthma. Chin J Pract Intern Med. 2014; 34:794-796.
33. Kocabas A, Avsar M, Hanta I, Koksal F, Kuleci S. Chlamydophila pneumoniae infection in adult asthmatics patients. J Asthma. 2008; 45:39-43.
34. Bébéar C, Raherison C, Nacka F, de Barbeyrac B, Pereyre S, Renaudin H, et al. Comparison of Mycoplasma pneumoniae infections in asthmatic children versus asthmatic adults. Pediatr Infect Dis J. 2014; 33:71-75.
35. Chen X, Zhang P, Ma Y. Prevalence of acute infection in adults with asthma exacerbation: A systematic review and meta-analysis. Ann Thorac Med. 2023; 18:132-151.
36. McCauley K, Durack J, Valladares R, Fadrosh DW, Lin DL, Calatroni A, et al. Distinct nasal airway bacterial microbiotas differentially relate to exacerbation in pediatric patients with asthma. J Allergy Clin Immunol. 2019; 144:1187-1197
37. Tang HHF, Lang A, Teo SM, Judd LM, Gangnon R, Evans MD, et al. Developmental patterns in the nasopharyngeal microbiome during infancy are associated with asthma risk. J Allergy Clin Immunol. 2021; 147:1683–1691.
38. Teo SM, Mok D, Pham K, Kusel M, Serralha M, Troy N, et al. The infant nasopharyngeal microbiome impacts severity of lower respiratory infection and risk of asthma development. Cell Host Microbe. 2015;17: 704–715
39. Fazlollahi M, Lee TD, Andrade J, Oguntuyo K, Chun Y, Grishina G, et al. The nasal microbiome in asthma. J Allergy Clin Immunol. 2018; 142:834-843.
40. Durack J, Lynch SV, Nariya S, Bhakta NR, Beigelman A, Castro M, et al. Features of the bronchial bacterial microbiome associated with atopy, asthma, and responsiveness to inhaled corticosteroid treatment. J Allergy Clin Immunol. 2017; 140:63-75.
41. Liu S, Lin Z, Zhou J, Yang X, You L, Yang Q, et al. Distinct Airway Microbiome and Metabolite Profiles in Eosinophilic and Neutrophilic Asthma. J Asthma Allergy. 2025; 18:1003-1022.

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42. Huang YJ, Nariya S, Harris JM, Lynch SV, Choy DF, Arron JR, et al. The airway microbiome in patients with severe asthma: Associations with disease features and severity. J Allergy Clin Immunol. 2015; 136:874-884.
43. McCauley KE, Flynn K, Calatroni A, DiMassa V, LaMere B, Fadrosh DW, et al. Seasonal airway microbiome and transcriptome interactions promote childhood asthma exacerbations. J Allergy Clin Immunol. 2022; 150:204-213.
44. Fahy JV, Dickey BF. Airway mucus function and dysfunction. N. Engl. J. Med. 2010; 363: 2233–2247.
45. Birchenough GMH, Johansson MEV, Gustafsson JK, Bergström JH, Hansson GC. New developments in goblet cell mucus secretion and function. Mucosal Immunol. 2015: 8;712–719.
46. Ma J, Rubin BK, Voynow JA. Sputum mucins, mucus, and goblet cells. Chest. 2018; 154:169–176.
47. Bonser LR, Erle DJ. The airway epithelium in asthma. Adv Immunol. 2019; 142: 1–34.
48. Lachowicz-Scroggins ME, Yuan S, Kerr SC, Dunican EM, Yu M, Carrington SD, et al. Abnormalities in MUC5AC and MUC5B protein in airway mucus in asthma. Am J Respir Crit Care Med. 2016; 194:1296–1299.
49. Parker D, Ahn D, Cohen T, Prince A. Innate immune signaling activated by MDR bacteria in the airway. Physiol Rev. 2016; 96: 19–53.
50. Schleimer RP, Kato A, Kern R, Kuperman D, Avila PC. Epithelium: at the interface of innate and adaptive immune responses. J Allergy Clin Immunol. 2007; 120:1279-1284.
51. Di YP, Kuhn JM, Mangoni M. Lung antimicrobial proteins and peptides: from host defense to therapeutic strategies. Physiol Rev. 2024; 104:1643-1677.
52. Semple F, Dorin JR. Beta-Defensins: multifunctional modulators of infection, inflammation and more? J Innate Immun. 2014;4: 337–348.
53. Hazlett L, Wu M. Defensins in innate immunity. Cell Tissue Res. 2011; 343: 175–188.
54. Vandamme D, Landuyt B, Luyten W, Schoofs L A comprehensive summary of LL-37, the factotum human cathelicidin peptide. Cell Immunol. 2012; 280: 22–35.
55. Oppenheim FG, Xu T, McMillian FM, Levitz SM, Diamond RD, Offner GD, et al. Histatins, a novel family of histidine-rich proteins in human parotid secretion. Isolation, characterization, primary structure, and fungistatic effects on Candida albicans. J Biol Chem. 1988; 263: 7472–7477.
56. Majchrzak-Gorecka M, Majewski P, Grygier B, Murzyn K, Cichy J. Secretory leukocyte protease inhibitor (SLPI), a multifunctional protein in the host defense response. Cytokine Growth Factor Rev. 2016;28: 79–93.
57. Berlutti F, Pantanella F, Natalizi T, Frioni A, Paesano R, Polimeni A, et al. Antiviral properties of lactoferrin–a natural immunity molecule. Molecules. 2011; 16: 6992–7018.
58. Cane J, Tregidgo L, Thulborn S, Finch D, Bafadhel M. Antimicrobial Peptides SLPI and Beta Defensin-1 in Sputum are Negatively Correlated with FEV1. Int J Chron Obstruct Pulmon Dis. 2021; 16:1437-1447.
59. Raundhal M, Morse C, Khare A, Oriss TB, Milosevic J, Trudeau J, et al. High IFN-gamma and low SLPI mark severe asthma in mice and humans. J Clin Invest. 2015;125: 3037–3050.
60. Thijs W, Janssen K, van Schadewijk AM, Papapoulos SE, le Cessie S, Middeldorp S, et al. Nasal Levels of Antimicrobial Peptides in Allergic Asthma Patients and Healthy Controls: Differences and Effect of a Short 1,25(OH)2 Vitamin D3 Treatment. PLoS One. 2015; 10:0140986. Ç
61. Beisswenger C, Kandler K, Hess C, Garn H, Felgentreff K, Wegmann M,et al. Allergic airway inflammation inhibits pulmonary antibacterial host defense. J Immunol. 2006; 177:1833-1837.
62. Negishi H, Taniguchi T, Yanai H. The Interferon (IFN) Class of Cytokines and the IFN Regulatory Factor (IRF) Transcription Factor Family. Cold Spring Harb Perspect Biol. 2018; 10:028423.
63. Wark PA, Johnston SL, Bucchieri F, Powell R, Puddicombe S, Laza-Stanca V, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J Exp Med 2005; 201:937-947.
64. Contoli M, Message SD, Laza-Stanca V, Edwards MR, Wark PA, Bartlett NW, et al. Role of deficient type III interferon-lambda production in asthma exacerbations. Nat Med. 2006; 12:1023-1026.

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65. Sykes A, Edwards MR, Macintyre J, del RA, Bakhsoliani E, Trujillo-Torralbo MB, et al. Rhinovirus 16-induced IFN-alpha and IFN-beta are deficient in bronchoalveolar lavage cells in asthmatic patients. J Allergy Clin Immunol. 2012; 129:1506-1514.
66. Baraldo S, Contoli M, Bazzan E, Turato G, Padovani A, Marku B, et al. Deficient antiviral immune responses in childhood: distinct roles of atopy and asthma. J Allergy Clin Immunol. 2012; 130:1307-1314.
67. Edwards MR, Regamey N, Vareille M, Kieninger E, Gupta A, Shoemark A, et al. Impaired innate interferon induction in severe therapy resistant atopic asthmatic children. Mucosal Immunol. 2013; 6:797-806.
68. Patel DA, You Y, Huang G, Byers DE, Kim HJ, Agapov E, et al. Interferon response and respiratory virus control are preserved in bronchial epithelial cells in asthma. J Allergy Clin Immunol. 2014; 134:1402-1412.
69. Sykes A, Macintyre J, Edwards MR, del RA, Haas J, Gielen V, et al. Rhinovirus-induced interferon production is not deficient in well controlled asthma. Thorax. 2014; 69:240-246.
70. Zhu J, Message SD, Mallia P, Kebadze T, Contoli M, Ward CK, et al. Bronchial mucosal IFN-α/β and pattern recognition receptor expression in patients with experimental rhinovirus-induced asthma exacerbations. J Allergy Clin Immunol. 2019; 143:114-125.
71. Gaberino CL, Altman MC, Gill MA, Bacharier LB, Gruchalla RS, O'Connor GT, et al. Dysregulation of airway and systemic interferon responses promotes asthma exacerbations in urban children. J Allergy Clin Immunol. 2025; 155:1499-1509.
72. Djukanovic R, Harrison T, Johnston SL, Gabbay F, Wark P, Thomson NC, et al. The effect of inhaled IFN-beta on worsening of asthma symptoms caused by viral infections. a randomized trial. Am J Respir Crit Care Med. 2014; 190:145–154.
73. Gay ACA, Banchero M, Carpaij O, Kole TM, Apperloo L, van Gosliga D, et al. Airway epithelial cell response to RSV is mostly impaired in goblet and multiciliated cells in asthma. Thorax. 2024; 79:811-821.
74. Cui H, Wang M, Jiao S, Tian S, Liu H, Luo B. Macrophages in chronic infections: regulation and remodeling. Front Immunol. 2025; 16:1594988.
75. Britt RD Jr, Ruwanpathirana A, Ford ML, Lewis BW. Macrophages Orchestrate Airway Inflammation, Remodeling, and Resolution in Asthma. Int J Mol Sci. 2023; 24:10451.
76. Draijer C, Boorsma CE, Robbe P, et al. Human asthma is characterized by more IRF5þ M1 and CD206þ M2 macrophages and less IL-10þ M2-like macrophages around airways compared with healthy airways. J Allergy Clin Immunol. 2017; 140:280–283.
77. Grunwell JR, Stephenson ST, Tirouvanziam R, Brown LAS, Brown MR, Fitzpatrick AM. Children with Neutrophil-Predominant Severe Asthma Have Proinflammatory Neutrophils With Enhanced Survival and Impaired Clearance. J Allergy Clin Immunol Pract. 2019; 7:516-525.
78. Alexis NE, Soukup J, Nierkens S, Becker S. Association between airway hyperreactivity and bronchial macrophage dysfunction in individuals with mild asthma. Am J Physiol Lung Cell Mol Physiol. 2001; 280:369-375.
79. Lay JC, Alexis NE, Zeman KL, Peden DB, Bennett WD. In vivo uptake of inhaled particles by airway phagocytes is enhanced in patients with mild asthma compared with normal volunteers. Thorax. 2009; 64:313-320.
80. Kulkarni N, Kantar A, Costella S, Ragazzo V, Piacentini G, Boner A, et al. Macrophage phagocytosis and allergen avoidance in children with asthma. Front Pediatr. 2018; 6:206.
81. Mace EM. Human natural killer cells: Form, function, and development. J Allergy Clin Immunol. 2023; 151:371-385.
82. Pianigiani T, Paggi I, Cooper GE, Staples KJ, McDonnell M, Bergantini L. Natural killer cells in the lung: novel insight and future challenge in the airway diseases. ERJ Open Res. 2025; 1:00683-2024.
83. Devulder J, Chenivesse C, Ledroit V, Fry S, Lobert PE, Hober D, et al. Aberrant anti-viral response of natural killer cells in severe asthma. Eur Respir J. 2020; 55:1802422.
84. Lepretre F, Gras D, Chanez P, Duez C. Natural killer cells in the lung: potential role in asthma and virus-induced exacerbation? Eur Respir Rev. 2023; 32:230036.
85. Fahy JV, Kim KW, Liu J. Boushey H.A. Prominent neutrophilic inflammation in sputum from subjects with asthma exacerbation. J. Allergy Clin. Immunol. 1995; 95: 843–852.

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Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 September 2025 doi:10.20944/preprints202509.1855.v1

86. Crisford H, Sapey E, Rogers GB, Taylor S, Nagakumar P, Lokwani R, et al. Neutrophils in asthma: the good, the bad and the bacteria. Thorax. 2021; 76:835–844.
87. Kuks PJM, Kole TM, Kraft M, Siddiqui S, Fabbri LM, Rabe KF, et al. Neutrophilic inflammation in sputum or blood does not define a clinically distinct asthma phenotype in ATLANTIS. ERJ Open Res. 2025; 11:00616-2024.
88. Ravindran M, Khan MA, Palaniyar N. Neutrophil Extracellular Trap Formation: Physiology, Pathology, and Pharmacology. Biomolecules. 2019; 9:365.
89. Cheng OZ, Palaniyar N. NET balancing: a problem in inflammatory lung diseases. Front Immunol. 2013; 4:1.
90. Dworski R, Simon HU, Hoskins A, Yousefi S. Eosinophil and neutrophil extracellular DNA traps in human allergic asthmatic airways. J Allergy Clin Immunol. 2011; 127:1260-1266.
91. Alexis NE, Eldridge MW, Peden DB. Effect of inhaled endotoxin on airway and circulating inflammatory cell phagocytosis and CD11b expression in atopic asthmatic subjects**.** J Allergy Clin Immunol. 2003; 112: 353–361.
92. McDowell PJ, Azim A, Busby J, Diver S, Yang F, Borg C, et al. Medical Research Council UK Refractory Asthma Stratification Programme (RASP-UK Consortium). Analysis of airway inflammation demonstrates a mechanism for T2-biologic failure in asthma. J Allergy Clin Immunol. 2025;29:S0091-6749(25)00696-7 Epub ahead of print.
93. Zambrano F, Uribe P, Schulz M, Hermosilla C, Taubert A, Sánchez R. Antioxidants as Modulators of NETosis: Mechanisms, Evidence, and Therapeutic Potential. Int J Mol Sci. 2025; 26:5272.
94. Tonello S, Vercellino N, D'Onghia D, Fracchia A, Caria G, Sola D, et al. Extracellular Traps in Inflammation: Pathways and Therapeutic Targets. Life (Basel). 2025; 15:627.
95. Anson C, Bjermer L, Lehtimäki L, Kankaanranta H, Karjalainen J, Altraja A, et al. Eosinophilic airway diseases: basic science, clinical manifestations and future challenges. Eur Clin Respir J. 2022; 9:2040707.
96. Kerkhof M, Tran TN, van den Berge M, Brusselle GG, Gopalan G, Jones RCM, et al. Association between blood eosinophil count and risk of readmission for patients with asthma:Historical cohort study. PLoS One. 2018; 13:0201143.
97. Jackson DJ, Akuthota P, Roufosse F. Eosinophils and eosinophilic immune dysfunction in health and disease. Eur Respir Rev. 2022; 31:210150.
98. Pope SM, Brandt EB, Mishra A, Hogan SP, Zimmermann N, Matthaei KI, et al. IL-13 induces eosinophil recruitment into the lung by an IL-5-and eotaxin-dependent mechanism. J Allergy Clin Immunol. 2001; 108:594-601.
99. Kandikattu HK, Upparahalli Venkateshaiah S, Mishra A. Synergy of interleukin (IL)-5 and IL-18 in eosinophil mediated pathogenesis of allergic diseases. Cytokine Growth Factor Rev. 2019; 47:83-98.
100. Piñeros YS S, Bal SM, Dijkhuis A, Majoor CJ, Dierdorp BS, Dekker T, et al. Eosinophils capture viruses, a capacity that is defective in asthma. Allergy. 2019; 74:1898–1909.
101. Rosenberg HF, Domachowske JB. Eosinophils, eosinophil ribonucleases, and their role in host defense against respiratory virus pathogens. J Leukoc Biol. 2001; 70:691–698.
102. Fujieda S, Imoto Y, Kato Y, Ninomiya T, Tokunaga T, Tsutsumiuchi T, et al. Eosinophilic chronic rhinosinusitis. Allergol Int. 2019; 68:403–412.
103. Barroso MV, Gropillo I, Detoni MAA, Thompson-Souza GA, Muniz VS, Vasconcelos CRI, et al. Structural and signaling events driving Aspergillus fumigatus-induced human eosinophil extracellular trap release. Front Microbiol. 2021; 12:633696.
104. Sasaki H, Miyata J, Kawana A, Fukunaga K. Antiviral roles of eosinophils in asthma and respiratory viral infection. Front Allergy. 2025; 6:1548338.
105. Dill-McFarland KA, Schwartz JT, Zhao H, Shao B, Fulkerson PC, Altman MC, et al. Eosinophil-mediated suppression and anti-IL-5 enhancement of plasmacytoid dendritic cell interferon responses in asthma. J Allergy Clin Immunol. 2022; 150:666–675.
106. Hatchwell L, Collison A, Girkin J, Parsons K, Li J, Zhang J, et al. Toll-like receptor 7
1. governs interferon and inflammatory responses to rhinovirus and is suppressed by
2. IL-5-induced lung eosinophilia. Thorax. 2015; 70:854-861.

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107. Veerati PC, Troy NM, Reid AT, Li NF, Nichol KS, Kaur P, et al. Airway Epithelial Cell Immunity Is Delayed During Rhinovirus Infection in Asthma and COPD. Front Immunol. 2020:15; 11:974.
108. Contoli M, Message SD, Laza-Stanca V, Edwards MR, Wark PA, Bartlett NW, et al. Role of deficient type III interferon-lambda production in asthma exacerbations. Nat Med. 2006; 12:1023-1026
109. Li NS, Yeh YW, Li L, Xiang Z. Mast cells: key players in host defense against infection. Scand J Immunol. 2025; 102:70046.
110. Portales-Cervantes L, Crump OM, Dada S, Liwski CR, Gotovina J, Haidl ID, et al. IL-4 enhances interferon production by virus-infected human mast cells. J Allergy Clin Immunol. 2020; 146:675-677.
111. Barra J, Liwski CR, Phonchareon P, Portales-Cervantes L, Gaston D, Karakach TK, et al. IL-5 enhances human mast cell survival and interferon responses to viral infection. J Allergy Clin Immunol. 2025; 155:1968-1980.
112. Lam N, Lee Y, Farber DL. A guide to adaptive immune memory. Nat Rev Immunol. 2024; 24:810-829.
113. Bousfiha A, Moundir A, Tangye SG, Picard C, Jeddane L, Al-Herz W, et al. The 2022 Update of IUIS Phenotypical Classification for Human Inborn Errors of Immunity. J Clin Immunol. 2022; 42:1508-1520.
114. Gerek ME, Colkesen F, Onalan T, Akkus FA, Kilinc M, Evcen R, et al. Selective immunoglobulin E deficiency and its association with autoimmune and autoinflammatory diseases. Allergy Asthma Proc. 2025; 46:91-97.
115. Agress A, Oprea Y, Roy S, Strauch C, Rosenstreich D, Ferastraoaru D. The Association Between Malignancy, Immunodeficiency, and Atopy in IgE-Deficient Patients. J Allergy Clin Immunol Pract. 2024; 12:185-194.
116. Noonan E, Straesser MD, Makin T, Williams A, Al-Hazaymeh A, Routes JM, et al. Impaired Response to Polysaccharide Vaccine in Selective IgE Deficiency. J Clin Immunol. 2023; 43:1448-1454.
117. Picado C, Ortiz de Landazuri I, Vlagea A, Bobolea I, Arismendi E, Amaro R, et al. Spectrum of Disease Manifestations in Patients with Selective Immunoglobulin E Deficiency. J Clin Med. 2021; 10:4160.
118. Schroeder HW Jr, Cavacini L. Structure and function of immunoglobulins. J Allergy Clin Immunol. 2010;125 (2 Suppl 2): 41-52.
119. Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, Cunningham-Rundles C, de la Morena MT, et al. International Consensus Document (ICON): Common Variable Immunodeficiency Disorders. J Allergy Clin Immunol Pract. 2016; 4:38-59.
120. Ameratunga R, Lehnert K, Woon ST. All patients with common variable immunodeficiency disorders (CVID) should be routinely offered diagnostic genetic testing. Front Immunol. 2019; 10:2678.
121. Moazzami B, Mohayeji Nasrabadi MA, Abolhassani H, Olbrich P, Azizi G, Shirzadi R, et al. Comprehensive assessment of respiratory complications in patients with common variable immunodeficiency. Ann Allergy Asthma Immunol. 2020; 124:505-511.
122. Filion CA, Taylor-Black S, Maglione PJ, Radigan L, Cunningham-Rundles C. Differentiation of Common Variable Immunodeficiency from IgG Deficiency. J Allergy Clin Immunol Pract. 2019; 7:1277-1284.
123. Bjelac JA, Blanch MB, Fernandez J. Allergic disease in patients with common variable immunodeficiency at a tertiary care referral center. Ann Allergy Asthma Immunol. 2018; 120:90-92.
124. Agondi RC, Barros MT, Rizzo LV, Kalil J, Giavina-Bianchi P. Allergic asthma in patients with common variable immunodeficiency. Allergy. 2010;65:510-515.
125. Rubin L, Shamriz O, Toker O, Kadish E, Ribak Y, Talmon A, et al. Allergic-like disorders and asthma in patients with common variable immunodeficiency: a multi-center experience. J Asthma. 2022; 59:476-483.
126. Milota T, Bloomfield M, Parackova Z, Sediva A, Bartunkova J, Horvath R. Bronchial Asthma and Bronchial Hyperresponsiveness and Their Characteristics in Patients with Common Variable Immunodeficiency. Int Arch Allergy Immunol. 2019; 178:192-200.
127. Urm SH, Yun HD, Fenta YA, Yoo KH, Abraham RS, Hagan J, et al. Asthma and risk of selective IgA deficiency or common variable immunodeficiency: a population-based case-control study. Mayo Clin Proc. 2013; 88:813-21.
128. Correa-Jimenez O, Restrepo-Gualteros S, Nino G, Cunningham-Rundles C, Sullivan KE, Fuleihan RL, et al. Respiratory Comorbidities Associated with Bronchiectasis in Patients with Common Variable Immunodeficiency in the USIDNET Registry. J Clin Immunol. 2023; 43:2208-2220.

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129. Ozcan C, Metin A, Erkocoglu M, Kocabas CN. Bronchial hyperreactivity in children with antibody deficiencies. Allergol Immunopathol (Madr). 2015; 43:57–61.
130. Ibrahim H, Walsh J, Casey D, Murphy J, Plant BJ, O'Leary P, et al. Recurrent asthma exacerbations: co-existing asthma and common variable immunodeficiency. J Asthma. 2022; 59:1177-1180.
131. Akaba T, Kondo M, Toriyama M, Kubo A, Hara K, Yamada T, et al. Common variable immunodeficiency diagnosed during the treatment of bronchial asthma: Unusual cause of wheezing. Respir Med Case Rep. 2015; 16:41-44.
132. Petrov AA, Adatia A, Jolles S, Nair P, Azar A, Walter JE. Antibody Deficiency, Chronic Lung Disease, and Comorbid Conditions: A Case-Based Approach. J Allergy Clin Immunol Pract. 2021; 9:3899-3908
133. Tiotiu A, Salvator H, Jaussaud R, Jankowski R, Couderc L-J, Catherinot E, et al. Efficacy of immunoglobulin replacement therapy and azithromycin in severe asthma with antibody deficiency. Allergol Int 2020; 69:215-222.
134. Barton JC, Barton JC, Bertoli LF, Acton RT. Factors associated with IgG levels in adults with IgG subclass deficiency. BMC Immunol. 2021; 22:53.
135. Ayres JG, Thompson RA. Low IgG subclass levels in brittle asthma and in patients with exacerbations of asthma associated with respiratory infection. Respir Med. 1997; 91:464-469.
136. Visca D, Ardesi F, Centis R, Pignatti P, Spanevello A. Brittle Asthma: Still on Board? Biomedicines. 2023; 11:3086.
137. Abrahamian F, Agrawal S, Gupta S. Immunological and clinical profile of adult patients with selective immunoglobulin subclass deficiency: response to intravenous immunoglobulin therapy. Clin Exp Immunol. 2010; 159:344-350.
138. Vivarelli E, Perlato M, Accinno M, Brugnoli B, Milanese ME, Cataudella E, et al. Asthma Phenotype Can Be Influenced by Recurrent Respiratory Infections in Patients with Primary Antibody Deficiency: The Impact of Ig Therapy. Respiration. 2025; 104:457-465.
139. Kim JH, Ye YM, Ban GY, Shin YS, Lee HY, Nam YH, et al. Effects of Immunoglobulin Replacement on Asthma Exacerbation in Adult Asthmatics with IgG Subclass Deficiency. Allergy Asthma Immunol Res. 2017; 9:526-533.
140. Hatcher VR, Alix VC, Hellu TS, Schuldt MM. Primary Immunodeficiency: Specific antibody deficiency with normal IgG. Allergy Asthma Proc. 20241; 45:321-325.
141. Perrard N, Stabler S, Sanges S, Terriou L, Lamblin C, Gaillard S, et al. Diagnosis, Characteristics, and Outcome of Selective Anti-polysaccharide Antibody Deficiencies in a Retrospective Cohort of 55 Adult Patients. J Clin Immunol. 2025; 45:82.
142. Bonilla FA, Khan DA, Ballas ZK, Chinen J, Frank MM, Hsu JT, et al. Practice Parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. 2015; 136:1186–1205.
143. Keswani A, Dunn NM, Manzur A, Kashani S, Bossuyt X, Grammer LC, et al. The Clinical Significance of Specific Antibody Deficiency (SAD) Severity in Chronic Rhinosinusitis (CRS). J Allergy Clin Immunol Pract. 2017; 5:1105-1111.
144. Schwartz HJ, Hostoffer RW, McFadden ER Jr, Berger M. The response to intravenous immunoglobulin replacement therapy in patients with asthma with specific antibody deficiency. Allergy Asthma Proc. 2006; 27:53-58.
145. Weber-Mzell D, Kotanko P, Hauer AC, Goriup,U, Haas J, Lanner N, et al. Gender, age and seasonal effects on IgA deficiency: A study of 7293 Caucasians. Eur. J. Clin. Investig. 2004; 34: 224–228.
146. Yel, L. Selective IgA deficiency. J. Clin. Immunol. 2010; 30:10–16
147. El-Sayed ZA, El-Ghoneimy DH, Ortega-Martell JA, Radwan N, Aldave JC, Al-Herz W, et al. Allergic manifestations of inborn errors of immunity and their impact on the diagnosis: a world-wide study. World Allergy Organ J. 2022; 15:100657.
148. Cunningham-Rundles C. Physiology of IgA and IgA Deficiency. J. Clin. Immunol. 2001; 21:303–330
149. Vosughimotlagh A, Rasouli SE, Rafiemanesh H, Safarirad M, Sharifinejad N, Madanipour A, et al. Clinical manifestation for immunoglobulin A deficiency: a systematic review and meta-analysis. Allergy Asthma Clin Immunol. 2023; 19:75.

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Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 September 2025 doi:10.20944/preprints202509.1855.v1

150. Pastorino AC, Accioly AP, Lanzellotti R, Camargo MC, Jacob CM, Grumach AS. Asthma - clinical and epidemiological aspects of 237 outpatients in a specialized pediatric unit. J Pediatr (Rio J). 1998; 74:4958.
151. Morawska I, Kurkowska S, B ̨ebnowska D, Hrynkiewicz R, Becht R, Michalski A, et al. The epidemiology and clinical presenta-tions of atopic diseases in selective IgA deficiency. J Clin Med. 2021; 10:3809.
152. Gupta, S.; Gupta, A. Defining Primary Selective IgM Deficiency. J. Clin. Immunol. 2019, 39, 350–352
153. Taietti I, Votto M, De Filippo M, Naso M, Montagna L, Montagna D, et al. Selective IgM Deficiency: Evidence, Controversies, and Gaps. Diagnostics (Basel). 2023; 13:2861.
154. Cassidy JT, Nordby GL. Human serum immunoglobulin concentrations: Prevalence of immunoglobulin deficiencies. J. Allergy Clin. Immunol. 1975; 55:35–48.
155. Entezari N, Adab Z, Zeydi M, Saghafi S, Jamali M, Kardar GA, et al. The prevalence of Selective Immunoglobulin M Deficiency (SIgMD) in Iranian volunteer blood donors. Hum. Immunol. 2016; 77: 7–11.
156. Caka C, Cimen O, Kahyaoglu P, Tezcan I, Cagdas, D. Selective IgM deficiency: Follow-up and outcome. Pediatr Allergy Immunol. 2021; 32:1327–1334.
157. Goldstein MF, Goldstein AL, Dunsky EH, Dvorin DJ, Belecanech GA, Shamir K. Pediatric Selective IgM Immunodeficiency. J. Immunol. Res. 2008; 2008:624850.
158. Lucuab-Fegurgur DL, Gupta S. Comprehensive clinical and immunological features of 62 adult patients with selective primary IgM deficiency. Am J Clin Exp Immunol. 2019; 8:55-67.
159. Chovancova Z, Kralickova P, Pejchalova A, Bloomfield M, Nechvatalova J, Vlkova M, et al. Selective IgM Deficiency: Clinical and Laboratory Features of 17 Patients and a Review of the Literature. J Clin Immunol. 2017; 37:559-574.
160. Goldstein MF, Goldstein AL, Dunsky EH, Dvorin DJ, Belecanech GA, Shamir K. Selective IgM immunodeficiency: retrospective analysis of 36 adult patients with review of the literature. Ann Allergy Asthma Immunol. 2006; 97:717-730.
161. Patel SS, Fergeson JE, Glaum MC, Lockey RF. Symptomatic Primary Selective Immunoglobulin M Deficiency with Nonprotective Pneumococcal Titers Responsive to Subcutaneous Immunoglobulin Treatment. Int. Arch. Allergy Immunol. 2016; 170:138–140.
162. Wu LC, Zarrin AA. The production and regulation of IgE by the immune system. Nat Rev Immunol. 2014; 14:247-259.
163. Vinnes EW, Røys EÅ, Renstrøm R, Karlsen Sletten IS, Chakraborty S. A systematic review of total IgE reference intervals - A 2024 update. Clin Chim Acta. 2025; 566:120024.
164. Lawrence MG, Palacios-kibler T V, Workman LJ, Alexander J, Steinke JW, Payne SC, et al. Low Serum IgE is a Sensitive and Specific Marker for Common Variable Immunodeficiency (CVID). J Clin Immunol. 2019; 38:225–233.
165. Smith JK, Krishnaswamy GH, Dykes R, Reynolds S, Berk SL. Clinical manifestations of IgE hypogammaglobulinemia. Ann Allergy Asthma Immunol. 1997; 78:313-318.
166. Magen E, Schlesinger M, David M, Ben-Zion I, Vardy D. Selective IgE deficiency, immune dysregulation, and autoimmunity. Allergy Asthma Proc. 2014; 35:27-33.
167. Ünsal H, Ekinci A, Aliyeva G, Bildik HN, Esenboğa S, Çağdaş D. Characteristics of patients with low serum IgE levels and selective IgE deficiency: Data from an immunodeficiency referral center. Clin Immunol. 2025;270:110403.
168. Picado C, García-Herrera AP, Hernández-Rodríguez J, Vlagea A, Pascal M, Bartra J, et al. Skin Manifestations in Patients with Selective Immunoglobulin E Deficiency. J Clin Med. 2022; 11:6795.
169. Nemet S, Elbirt D, Cohen R, Mahlab-Guri K, Bezalel-Rosenberg S, Asher I, et al. IgE deficiency (2.5 IU/mL) in children: Clinical insights from a population-based study of 123,393 subjects. Pediatr Allergy Immunol. 2025; 36:70092.
170. Zhang J, Ni J, Kong W, Liu J, Chen Y. Various clinical manifestations of 223 patients with IgE deficiency in a tertiary hospital in China: A cross-sectional study. Medicine (Baltimore). 2024;103: 38397.
171. Ferastraoaru, D.; Goodman, B.; Rosenstreich, D. Higher rates of malignancy in patients with immunoglobulin E deficiency and negative immediate hypersensitivity skin tests. Ann. Allergy Asthma Immunol. 2021; 126:194–195

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172. Ferastraoaru, D.; Schwartz, D.; Rosenstreich, D. Increased Malignancy Rate in Children With IgE Deficiency: A Single-center Experience. J Pediatr Hematol Oncol. 2021; 43:472–477.
173. Uygun DFK, Uygun V, Başaran A, Kocatepe G, Kazlı T, Bingöl A. High malignancy rate in IgE-deficient children. Int J Cancer. 2025; 156:964-968.
174. Noonan E, Straesser MD, Makin T, Williams A, Al-Hazaymeh A, Routes JM, et al. Impaired Response to Polysaccharide Vaccine in Selective IgE Deficiency. J Clin Immunol. 2023; 43:1448-1454.
175. Beisswenger C, Kandler K, Hess C, Garn H, Felgentreff K, Wegmann M,et al. Allergic airway inflammation inhibits pulmonary antibacterial host defense. J Immunol. 2006; 177:1833-1837.
176. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. Am J Respir Crit Care Med. 2001;164(8 Pt 1):1392-1397.
177. Pauwels RA, Löfdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. N Engl J Med. 1997; 337:1405-1411.
178. Edwards MR, Haas J, Panettieri RA Jr, Johnson M, Johnston SL. Corticosteroids and beta2 agonists differentially regulate rhinovirus-induced interleukin-6 via distinct Cis-acting elements. J Biol Chem. 2007; 282:15366-15375
179. Van Ly D, King NJ, Moir LM, Burgess JK, Black JL, Oliver BG. Effects of β2 Agonists, Corticosteroids, and Novel Therapies on Rhinovirus-Induced Cytokine Release and Rhinovirus Replication in Primary Airway Fibroblasts. J Allergy (Cairo). 2011; 2011:457169.
180. Kan-O K, Washio Y, Oki T, Fujimoto T, Ninomiya T, Yoshida M, et al. Effects of treatment with corticosteroids on human rhinovirus-induced asthma exacerbations in pediatric inpatients: a prospective observational study. BMC Pulm Med. 2023; 23:487.
181. Tacon CE, Newton R, Proud D, Leigh R. Rhinovirus-induced MMP-9 expression is dependent on Fra-1, which is modulated by formoterol and dexamethasone. J Immunol. 2012; 188:4621-30.
182. Skevaki CL, Christodoulou I, Spyridaki IS, Tiniakou I, Georgiou V, Xepapadaki P, et al. Budesonide and formoterol inhibit inflammatory mediator production by bronchial epithelial cells infected with rhinovirus. Clin Exp Allergy. 2009; 39:1700-10.
183. Maeda K, Caldez MJ, Akira S. Innate immunity in allergy. Allergy 2019; 74:1660–1674.
184. Nasiri Kalmarzi R, Fakhimi R, Manouchehri F, Ataee P, Naleini N. Babaei E, et al. The relationship between B7 homologous 1 with interleukin-4, interleukin-17 and interferon gamma in patients with allergic rhinitis. Expert Rev. Clin. Immunol. 2019; 15: 897–901.
185. Contoli M, Ito K, Padovani A, Poletti D, Marku B, Edwards MR, et al. Th2 cytokines impair innate immune responses to rhinovirus in respiratory epithelial cells. Allergy. 2015; 70:910-920.
186. Grutters J, Brinkman L, Aslander M, van den Bosch J, Koenderman L, Lammers J. Asthma therapy modulates priming-associated blood eosinophil responsiveness in allergic asthmatics. Eur Respir J. 1999; 14:915-922.
187. Berthon BS, Gibson PG, Wood LG, et al. A sputum gene expression signature predicts oral corticosteroid response in asthma. Eur Respir J 2017; 49: 1700180.
188. Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, et al. Efficacy of azithromycin in severe asthma from the AMAZES randomised trial. ERJ Open Res. 01923; 5:00056-2019.
189. Thomas D, McDonald VM, Stevens S, Baraket M, Hodge S, James A, et al. Effect of
3. Azithromycin on Asthma Remission in Adults with Persistent Uncontrolled Asthma: A Secondary Analysis of a Randomized, Double-Anonymized, Placebo-Controlled Trial. Chest. 2024; 166:262-270.
190. Taylor SL, Leong LEX, Mobegi FM, Choo JM, Wesselingh S, Yang IA, et al. Long-Term Azithromycin Reduces Haemophilus influenzae and Increases Antibiotic Resistance in Severe Asthma. Am J Respir Crit Care Med. 2019; 200:309-317.
191. Lavoie G, Howell I, Melhorn J, Borg C, Bermejo-Sanchez L, Seymour J, et al. Effects of azithromycin in severe eosinophilic asthma with concomitant monoclonal antibody treatment. Thorax. 2025; 80:113-116
192. Ghanizada M, Malm Tillgren S, Praeger-Jahnsen L, Said NM, Ditlev S, et al. Effects of in vitro azithromycin treatment on bronchial epithelial antiviral immunity in asthma phenotypes. Front Allergy. 2025; 6:1605109.

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Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 September 2025 doi:10.20944/preprints202509.1855.v1

193. Gielen V, Johnston SL, Edwards MR. Azithromycin induces anti-viral responses in bronchial epithelial cells. Eur Respir J. 2010; 36:646-654.
194. Niessen NM, Gibson PG, Baines KJ, Barker D, Yang IA, Upham JW, et al. Sputum TNF markers are increased in neutrophilic and severe asthma and are reduced by azithromycin treatment. Allergy. 2021; 76:2090-2101.
195. Lin SJ, Lee WJ, Liang YW, Yan DC, Cheng PJ, Kuo ML. Azithromycin inhibits IL-5 production of T helper type 2 cells from asthmatic children. Int Arch Allergy Immunol. 2011; 156:179-186.
196. MacDonald KM, Kavati A, Ortiz B, Alhossan A, Lee CS, Abraham I. Short- and long-term real-world effectiveness of omalizumab in severe allergic asthma: systematic review of 42 studies published 2008-2018. Expert Rev Clin Immunol. 2019; 15:553-569.
197. Bousquet J, Humbert M, Gibson PG, Kostikas K, Jaumont X, Pfister P, et al. Real-World Effectiveness of Omalizumab in Severe Allergic Asthma: A Meta-Analysis of Observational Studies. J Allergy Clin Immunol Pract. 2021; 9:2702-2714.
198. van Rensen EL, Evertse CE, van Schadewijk WA, van Wijngaarden S, Ayre G,Mauad T, et al. Eosinophils in bronchial mucosa of asthmatics after allergen challenge: effect of anti-IgE treatment. Allergy. 2009; 64:72-80.
199. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med. 2011;17; 364:1005-1015.
200. Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes SJ Jr, Calatroni A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. J Allergy Clin Immunol. 2015; 136:1476-1485.
201. Kantor DB, McDonald MC, Stenquist N, Schultz BJ, Smallwood CD, Nelson KA, et al. Omalizumab Is Associated with Reduced Acute Severity of Rhinovirus-triggered Asthma Exacerbation. Am J Respir Crit Care Med. 2016; 194:1552-1555.
202. Esquivel A, Busse WW, Calatroni A, Togias AG, Grindle KG, Bochkov YA, et al. Effects of Omalizumab on Rhinovirus Infections, Illnesses, and Exacerbations of Asthma. Am J Respir Crit Care Med. 2017;15; 196:985-992
203. Ke X, Kavati A, Wertz D, Huang Q, Wang L, Willey VJ, et al. Real-world Clinical Characteristics, Treatment Patterns, and Exacerbations in US Patients with Asthma Newly Treated With Omalizumab. Clin Ther. 2018; 40:1140-1158.
204. Gill MA, Liu AH, Calatroni A, Krouse RZ, Shao B, Schiltz A, et al. Enhanced plasmacytoid dendritic cell antiviral responses after omalizumab. J Allergy Clin Immunol. 2018; 141:1735-1743.
205. Sheehan WJ, Krouse RZ, Calatroni A, Gergen PJ, Gern JE, Gill MA, et al. Aeroallergen Sensitization, Serum IgE, and Eosinophilia as Predictors of Response to Omalizumab Therapy During the Fall Season Among Children with Persistent Asthma. J Allergy Clin Immunol Pract. 2020; 8:3021-3028.
206. Deeks ED. Mepolizumab: A Review in Eosinophilic Asthma. BioDrugs. 2016; 30:361-370.
207. Deeks ED, Brusselle G. Reslizumab in Eosinophilic Asthma: A Review. Drugs. 2017; 77:777-784.
208. Chupp GL, Bradford ES, Albers FC, Bratton DJ, Wang-Jairaj J, Nelsen LM, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. Lancet Respir Med. 2017; 5:390–400.
209. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014; 371:1198-1207.
210. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012; 380:651-659.
211. Pilette C, Canonica GW, Chaudhuri R, Chupp G, Lee FE, Lee JK, et al. REALITI-A Study: Real-World Oral Corticosteroid-Sparing Effect of Mepolizumab in Severe Asthma. J Allergy Clin Immunol Pract. 2022; 10:2646-2656.
212. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med. 2015; 3:355-366.

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Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 September 2025 doi:10.20944/preprints202509.1855.v1

213. Jackson DJ, Bacharier LB, Gergen PJ, Gagalis L, Calatroni A, Wellford S, et al. Mepolizumab for urban children with exacerbation-prone eosinophilic asthma in the USA (MUPPITS-2): a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet. 2022; 400:502-511.
214. Dill-McFarland KA, Schwartz JT, Zhao H, Shao B, Fulkerson PC, Altman MC, et al. Eosinophil-mediated suppression and anti-IL-5 enhancement of plasmacytoid dendritic cell interferon responses in asthma. J Allergy Clin Immunol. 2022; 150:666-675.
215. Sabogal Piñeros YS, Bal SM, van de Pol MA, Dierdorp BS, Dekker T, Dijkhuis A, et al. Anti-IL-5 in Mild Asthma Alters Rhinovirus-induced Macrophage, B-Cell, and Neutrophil Responses (MATERIAL). A Placebo-controlled,Double-Blind Study. Am J Respir Crit Care Med. 2019; 199:508-517.
216. Domvri K, Tsiouprou I, Bakakos P, Steiropoulos P, Katsoulis K, Kostikas K, et al. Effect of mepolizumab in airway remodeling in patients with late-onset severe asthma with an eosinophilic phenotype. J Allergy Clin Immunol. 2025; 155:425-435.
217. Matera MG, Calzetta L, Rinaldi B, Cazzola M. Pharmacokinetic/pharmacodynamic drug
4. evaluation of benralizumab for the treatment of asthma. Expert Opin Drug Metab Toxicol.
5. 2017; 13:1007-1013.
218. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β₂-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet. 2016;29; 388:2115-2127.
219. Korn S, Bourdin A, Chupp G, Cosio BG, Arbetter D, Shah M, et al. Integrated Safety and Efficacy Among Patients Receiving Benralizumab for Up to 5 Years. J Allergy Clin Immunol Pract. 2021; 9:4381-4392.
220. DuBuske L, Newbold P, Wu Y, Trudo F. Seasonal variability of exacerbations of severe, uncontrolled eosinophilic asthma and clinical benefits of benralizumab. Allergy Asthma Proc. 2018; 39:345-349.
221. McCann MR, Kosloski MP, Xu C, Davis JD, Kamal MA. Dupilumab: Mechanism of
6. action, clinical, and translational science. Clin Transl Sci. 2024; 17:13899.
222. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018;28; 378:2486-2496.
223. Geng B, Bachert C, Busse WW, Gevaert P, Lee SE, Niederman MS, et al. Respiratory Infections and Anti-Infective Medication Use from Phase 3 Dupilumab Respiratory Studies. J Allergy Clin Immunol Pract. 2022; 10:732-741.
224. Peters AT, Sagara H, Corren J, Domingo C, Altincatal A, Soler X, et al. Impact of dupilumab across seasons in patients with type 2, uncontrolled, moderate-to-severe asthma. Ann Allergy Asthma Immunol. 2024; 132:477-484.
225. Boomer J, Choi J, Alsup A, McGregor MC, Lieu J, Johnson C, et al. Increased Muc5AC and Decreased Ciliated Cells in Severe Asthma Partially Restored by Inhibition of IL-4Rα Receptor. Am J Respir Crit Care Med. 2024; 210:1409-1420.
226. Murai Y, Koya T, Koda H, Uji W, Tanaka M, Endo M, et al. Dupilumab efficacy in relation to changes in club cell secretory protein 16. Ann Allergy Asthma Immunol. 2025; 134:556-562.
227. Martinu T, Todd JL, Gelman AE, Guerra S, Palmer SM. Club cell secretory protein (CCSP/SCGB1A1) in lung disease: emerging concepts and potential therapeutics. Annu Rev Med 2023; 74:427–441.
228. Gauvreau GM, Sehmi R, Ambrose CS, Griffiths JM. Thymic stromal lymphopoietin:its role and potential as a therapeutic target in asthma. Expert Opin Ther Targets. 2020; 24:777-792.
229. Lugogo NL, Akuthota P, Sumino K, Mathur SK, Burnette AF, Lindsley AW, et al. Effectiveness and Safety of Tezepelumab in a Diverse Population of US Patients with Severe Asthma: Initial Results of the PASSAGE Study. Adv Ther. 2025; 42:3334-3353.
230. Diver S, Khalfaoui L, Emson C, Wenzel SE, Menzies-Gow A, Wechsler ME, et al. Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled,phase 2 trial. Lancet Respir Med. 2021; 9:1299-1312.

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231. Corren J, Menzies-Gow A, Chupp G, Israel E, Korn S, Cook B, et al. Efficacy of Tezepelumab in Severe, Uncontrolled Asthma:Pooled Analysis of the PATHWAY and NAVIGATOR Clinical Trials. Am J Respir Crit Care Med. 2023; 208:13-24
232. Pavord ID, Hoyte FCL, Lindsley AW, Ambrose CS, Spahn JD, Roseti SL, et al. Tezepelumab reduces exacerbations across all seasons in patients with severe, uncontrolled asthma (NAVIGATOR). Ann Allergy Asthma Immunol. 2023; 131:587-597.
233. Sverrild A, Cerps S, Nieto-Fontarigo JJ, Ramu S, Hvidtfeldt M, Menzel M, et al. Tezepelumab decreases airway epithelial IL-33 and T2-inflammation in response to viral stimulation in patients with asthma. Allergy. 2024; 79:656-666.
234. van Heerden D, van Binnendijk RS, Tromp SAM, Savelkoul HFJ, van Neerven RJJ, den Hartog G. Asthma-Associated Long TSLP Inhibits the Production of IgA. Int J Mol Sci. 2021; 22:3592.
235. Lee SH, Ban GY, Kim SC, Chung CG, Lee HY, Lee JH, et al. Association between primary immunodeficiency and asthma exacerbation in adult asthmatics. Korean J Intern Med 2020; 35:449-56.
236. Lee SH, Ban GY, Kim SC, Chung CG, Lee HY, Lee JH, et al. Association between primary immunodeficiency and asthma exacerbation in adult asthmatics. Korean J. Intern. Med. 2020; 35: 449–456.
237. Jarjour NN, Erzurum SC, Bleecker ER, Calhoun WJ, Castro M, Comhair SA, et al. Severe asthma: lessons learned from the National Heart, Lung, and Blood Institute Severe Asthma Research Program. Am J Respir Crit Care Med. 2012; 185:356-362.
238. Tanosaki T, Kabata H, Matsusaka M, Miyata J, Masaki K, Mochimaru T, et al. Clinical characteristics of patients with not well-controlled severe asthma in Japan: Analysis of the Keio Severe Asthma Research Program in Japanese population (KEIO-SARP) registry. Allergol Int. 2021; 70:61-67.
239. Pembrey L, Barreto ML, Douwes J, Cooper P, Henderson J, Mpairwe H, et al. Understanding asthma phenotypes: the World Asthma Phenotypes (WASP) international collaboration. ERJ Open Res. 2018; 4:00013-2018.
240. Lee T, Kim J, Kim S, Kim K, Park Y, Kim Y, et al. Risk factors for asthma-related healthcare use: longitudinal analysis using the NHI claims database in a Korean asthma cohort. PLoS One. 2014; 9:112844
241. Simpson AJ, Hekking PP, Shaw DE, Fleming LJ, Roberts G, Riley JH, et al. Treatable traits in the European U-BIOPRED adult asthma cohorts. Allergy. 2019; 74:406-411.
242. Fahy JV, Jackson ND, Sajuthi SP, Pruesse E, Moore CM, Everman JL, et al. Type 1 Immune Responses Related to Viral Infection Influence Corticosteroid Response in Asthma. Am J Respir Crit Care Med. 2025; 211:194-204.
243. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier
244. L, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol. 2007; 119:405-13.

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