REVIEW

Phenotyping Asthma Exacerbations: One Step Further in the Management of Severe Asthma

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Abstract

Asthma, a prevalent chronic respiratory disease, manifests in heterogeneous phenotypes and endotypes, necessitating bespoke therapeutic approaches. Asthma exacerbations are characterized by worsening of symptoms and decline in lung function and present substantial challenges despite advances in understanding and treatment. Viral respiratory infections, notably those caused by rhinovirus, serve as primary triggers, with allergic sensitization and environmental exposures increasing susceptibility. Deficient antiviral responses in asthmatic airway epithelial cells, particularly impaired interferon production, perpetuate inflammation and hyperresponsiveness, contributing to exacerbations. Additionally, genetic polymorphisms influence host responses and susceptibility.

Recent studies underscore the association between specific inflammatory profiles, particularly eosinophil-mediated inflammation, and the frequency of exacerbations. Biologic therapies targeting inflammatory pathways show promise in reducing the frequency of exacerbations, thus underscoring the importance of understanding inflammatory phenotypes when selecting treatment. Notably, T2 inhibitors may modulate immune responses, potentially mitigating viral exacerbations.

Characterizing exacerbations is crucial for optimizing therapeutic strategies. Evidence suggests a dissociation between baseline inflammatory profiles and exacerbation phenotypes, highlighting the need for individualized management. Phenotyping exacerbations using sputum analysis helps to identify predominant inflammatory patterns and thus inform treatment decisions. The varied responses to biologic therapies further emphasize the importance of phenotyping exacerbations in refining treatment algorithms.

In conclusion, phenotyping asthma exacerbations provides valuable insights into underlying inflammatory mechanisms and enables personalized therapy. Understanding the complex interplay between viral triggers, inflammatory pathways, and responses to treatment is essential if we are to effectively manage severe asthma and reduce the burden of exacerbations. Further research into the mechanistic actions of biologic therapies in mitigating viral exacerbations is warranted to optimize asthma management strategies.

Key words: Severe asthma. Exacerbation. Phenotype. Biologic.

Resumen

El asma, una enfermedad respiratoria crónica prevalente, se manifiesta en fenotipos y endotipos heterogéneos, lo que requiere enfoques terapéuticos a medida. Las exacerbaciones asmáticas, caracterizadas por la exacerbación de los síntomas y la disminución de la función pulmonar, representan desafíos sustanciales a pesar de los avances en la comprensión y el tratamiento. Las infecciones respiratorias virales, en particular el rinovirus, actúan como desencadenantes primarios, mientras que la sensibilización alérgica y las exposiciones ambientales agravan la susceptibilidad. Las respuestas antivirales deficientes en las células epiteliales de las vías respiratorias asmáticas, particularmente la producción de interferón deteriorada, perpetúan la inflamación y la hiperreactividad, contribuyendo a las exacerbaciones. Además, los polimorfismos genéticos influyen en las respuestas y la susceptibilidad del huésped. Los estudios recientes subrayan la asociación entre perfiles inflamatorios específicos, en particular la inflamación mediada por eosinófilos, y la frecuencia de exacerbaciones. Las terapias biológicas dirigidas a las vías inflamatorias han mostrado gran eficacia en la reducción de exacerbaciones, enfatizando la importancia de comprender los fenotipos inflamatorios para guiar la selección de tratamientos. Notablemente, los inhibidores de T2 pueden modular las respuestas inmunitarias, lo que potencialmente mitiga las exacerbaciones inducidas por virus. Caracterizar las exacerbaciones es crucial para optimizar las estrategias terapéuticas. La evidencia sugiere una disociación entre los perfiles inflamatorios basales y los fenotipos de exacerbación, lo que destaca la necesidad de una gestión individualizada. El fenotipado de las exacerbaciones mediante el análisis de esputo ayuda a identificar patrones inflamatorios predominantes, facilitando las decisiones sobre el tratamiento más adecuado. Las distintas respuestas a las terapias biológicas destacan aún más la importancia del fenotipado de las exacerbaciones en el refinamiento de los algoritmos de tratamiento.

En conclusión, el fenotipado de las exacerbaciones asmáticas proporciona valiosos conocimientos sobre los mecanismos inflamatorios subyacentes, guiando intervenciones terapéuticas personalizadas. Comprender la compleja interacción entre los desencadenantes virales, las vías inflamatorias y las respuestas al tratamiento es esencial para gestionar eficazmente el asma grave y reducir la carga de las exacerbaciones. Son necesarios más estudios dirigidos a conocer la fisiología de las terapias biológicas en la mitigación de las exacerbaciones virales para optimizar las estrategias de manejo del asma.

Palabras clave: Asma severa. Exacerbación. Fenotipo. Biológico.

Introduction

Asthma is the most common chronic respiratory disease. It affects 6%-12% of the population in developed countries, impacting approximately 320 million individuals globally [1]. Traditionally recognized as being associated with atopy or allergic responses, asthma is now understood as a heterogeneous and multifactorial condition characterized by diverse phenotypes and endotypes [2]. Advances in understanding of the molecular processes involved in development and progression have emphasized the importance of identifying the inflammatory phenotypes of patients with asthma. Indeed, the classification of asthma focuses primarily on the inflammatory phenotype [3]. Specifically, asthma classifications often hinge on the presence or absence of eosinophil-mediated type 2 inflammation, driven either by allergic reactions (T_H2) or nonallergic mechanisms via type 2 innate lymphoid cells (ILC2) [2]. Current therapeutic approaches, particularly for severe asthma, aim to tailor treatments based on the inflammatory profile (T2-high vs T2-low), targeting specific molecules such as IgE, interleukin (IL) 5, IL-5 receptor (IL-5R), interleukin 4 receptor α subunit (IL-4Rα), and thymic stromal lymphopoietin (TSLP) [3]. Even though the frequency of asthma exacerbations has been reduced by about 50% through blockade of specific inflammatory pathways, recurrent exacerbations continue to pose significant challenges [2,4].

Exacerbations of asthma are characterized by a progressive increase in a series of symptoms, namely, shortness of breath, cough, wheezing, and chest tightness, as well as progressive decrease in lung function, and represent a worsening of the patient's usual condition requiring intensification of treatment [5]. Severe exacerbations are defined as a worsening of asthma symptoms that require either of 2 approaches: (*a*) treatment with systemic corticosteroids (tablets, suspension, or injection) or an increase from a stable maintenance dose for at least 3 days (for consistency, courses of corticosteroids separated by 1 week or more should be treated as separate severe exacerbations); (*b*) hospitalization or admission to the emergency respiratory care unit owing to asthma and need for systemic corticosteroids, in line with the American Thoracic Society/European Respiratory Society statement on severe exacerbations [5].

Asthma exacerbations have been repeatedly related to loss of pulmonary function, impairment of quality of life, need for systemic corticosteroids, and higher mortality [6-8]. They also constitute a significant social and economic burden on the health care system. In Spain, the average direct cost of asthma exacerbations among patients with severe asthma is €758.70 per exacerbation (95%CI, 556.8-1011.1), with 82% of this cost being attributable to hospitalizations. For episodes that require hospital admission, the average cost escalates to €4997 per exacerbation [9].

Asthma exacerbations arise from a multifaceted interaction between environmental exposures and individual host factors [10]. Respiratory viral infections, particularly those caused by rhinovirus, are the predominant triggers. Additional significant contributors include allergens and other types of inhalant exposures (ie, pollution). Allergic sensitization and exposure to allergens not only contribute directly to the disease, but also amplify susceptibility to respiratory viral infections. Such viruses target the airway epithelium and may lead to type 2 inflammation characterized by a predominance of eosinophils, which are key to the escalated inflammatory response. The presence of type 2 inflammation and corresponding elevations in specific biomarker levels significantly influence the risk and mechanisms of exacerbations. This association is further underscored by the reduced frequency of exacerbations when biologics that target inflammatory pathways are administered. Additionally, various genetic polymorphisms are linked to an increased likelihood of exacerbations [11].

Walsh et al [12] investigated the link between different types of inflammation in the airways and asthma exacerbation rates in patients with severe asthma. The authors focused on tracking eosinophil and neutrophil levels in sputum over a year. The findings revealed that individuals with consistently high eosinophil levels faced a higher risk of asthma exacerbations within the year than those without this inflammatory profile. This is also very apparent in the placebo arms of randomized controlled trials assessing biologics, which show that the higher the number of eosinophils in the blood, the higher the risk of exacerbation. However, the level of neutrophils did not show a similar impact on risk of exacerbation. Essentially, the study showed that a particular inflammatory profile marked by eosinophils is linked to more frequent severe asthma flare-ups, suggesting that targeting this inflammation could be key in managing difficult asthma cases. However, it should be noted that the inflammatory profile of asthma exacerbations is also linked to the type of triggering agent, as shown in Table 1. Cross-sectional research indicates the existence of an exacerbation-prone asthma phenotype and highlights the usefulness of blood eosinophils and plasma IL-6 as predictive biomarkers. Subsequent longitudinal studies have validated the exacerbation-prone phenotype, which is characterized by

Table 1. Airway Inflammatory Response to Common Elicitors of Asthma Exacerbations. Modified From Hargreave and Nair [79].

Eosinophilic	
Allergens	Occupational sensitizers (HMW and LMW agents)
	Corticosteroid reduction
	Nonsteroidal anti-inflammatory drugs
	Premenstrual asthma
	Chronic rhinosinusitis
	Thunderstorm asthma
Neutrophilic	
	Viral infections
	Bacterial infections
	Tobacco smoke
	Occupational exposures (LMW agents, irritants, endotoxins)
	Obesity
Mixed eosinophil/neutrophil	
	Viral infections
	Bacterial infections
	Occupational exposure
Unknown	
	Gastroesophageal reflux
	Genetic factors
	Stress and psychological factors

Abbreviations: HMW, high-molecular-weight; LMW, low-molecular-weight.

systemic metabolic dysregulation. IL-6 levels in the blood were significantly correlated with exacerbation-prone asthma, and both IL-6 and eosinophil counts were effective in predicting exacerbations across the entire sample of asthma patients [13].

The main culprits for asthma exacerbations are respiratory viruses, although the exact reasons why these viruses trigger exacerbations are not fully understood [14]. Since the 1970s, respiratory infections caused by viruses, predominantly human rhinovirus types A and C, have been identified as the primary triggers of asthma exacerbations [15]. Notably, 50% to 80% of exacerbations in adults are linked to viral infections, and rhinovirus has been particularly associated with exacerbations in children during the return to school and the September epidemic. This relationship between asthma exacerbations and viral infections prompts critical inquiries regarding the susceptibility of individuals with a T2 inflammatory phenotype to viral-induced exacerbations, the molecular mechanisms underlying these exacerbations, and the efficacy of existing asthma treatments in managing such episodes [15] (Table 1).

Search Strategy

A comprehensive bibliographic search of the PubMed and Scopus databases was conducted by all the authors. The selection criteria for the articles included relevance to the topic of asthma exacerbations, methodological quality, and publication date, with a preference for recent studies and relevant reviews.

Altered Immunity in Patients With Asthma

The airway epithelium is the target of viral infections, serving as both a physical barrier and an immunological defense mechanism orchestrating a balanced antiviral and inflammatory response [16]. In healthy individuals, respiratory viral infections trigger a T_H1 inflammatory response, promoting viral clearance through the release of specific cytokines such as type I interferons (IFN-α, IFN-β) and type III interferons (IFN-λ). Interferons hinder viral entry and proliferation, contributing to an efficient antiviral response [16,17]. However, patients with asthma exhibit altered immune responses, resulting in a higher risk of exacerbations. This altered response stems from dysregulated airway epithelium and affects both innate and adaptive antiviral defenses.

Connection Between Innate and Adaptive Defenses

In patients with asthma, the airway epithelium is more susceptible to injury and displays a reduced barrier function owing to a deconstruction produced by impaired expression of E-cadherin and tight junction proteins, alongside an increased basal cell proportion [18,19]. Another abnormality observed in asthma is the alteration of receptors involved in viral sensing [20], with diminished expression of pattern recognition receptors in patients with both mild asthma and severe asthma [21]. The reduction in these receptors contributes to increased susceptibility to viral infections in patients with asthma [22].

In asthma, bronchial epithelial cells exhibit defective production of antiviral INFs such as type 1 and type 3 in response to viral attacks, commonly referred to as host resistance [23-27]. IFN-β was found to be particularly deficient in patients with asthma compared to healthy individuals [28], whereas IFN-λ was found to play an essential role in the pathogenesis and clinical outcomes of virus-induced exacerbations. Although most studies support this deficiency, others suggest that patients with asthma [29] present preserved delayed antiviral responses compared to healthy individuals [25,30]. The exact mechanisms underlying INF deficiency in persons with asthma remain unknown, with hypotheses including polymorphisms in IFN genes or their promoters [31] and the suppressive actions of excess tumor growth factor (TGF) β on INF regulatory factor 3 pathways [32,33]. The physiologic functions of plasmacytoid dendritic cells are altered in young children with the persistent longitudinal exacerbation phenotype. Expression of high-affinity IgE receptors is increased, and their function as major INF producers is impaired during acute exacerbations of wheeze [27].

IFNs are key components in the innate immune response of the airway epithelium to viral infections. They exert a direct antiviral effect on infected and neighboring cells, while promoting acquired antiviral immune responses [34]. Production of IFN by epithelial cells is required for an effective antiviral response and viral clearance. For instance, IFN-β

induces apoptosis in virus-infected epithelial cells, a process that is significantly less common in patients with asthma than in the general population [28,35].

Epithelial cells not only possess direct antiviral properties by inhibiting viral replication, but also indirectly stimulate innate and adaptive immune responses. Airway epithelial cells from individuals with asthma exhibit an increased capacity to produce epithelial cytokines in response to viral infections, leading to downstream inflammatory responses and impaired host tolerance to viruses [36-38]. These cytokines, which are known as alarmins, include TSLP, IL-25, IL-33, and high mobility group box 1 (HMGB1), regulate immune cell populations, and activate T_H2- and ILC2-mediated inflammatory pathways, particularly in lung disorders such as childhood asthma [39-44].

Viral infection induces disproportionate expression of TSLP—compared with IFN-β—from bronchial epithelial cells in patients with asthma [36,45]. Experimental models of rhinovirus infection in asthma demonstrated increased levels of IL-33, which correlated with both IL-5 and IL-13 levels in the airway lining fluid and with severity of exacerbation following inoculation by the virus [46]. Similarly, experimental rhinovirus infection induced higher IL-25 production in individuals [47]. These alarmins directly stimulate ILC2s, releasing IL-4, IL-5, and IL-13, which are major mediators of the T2 inflammatory response [48,49]. Consequently, patients who display a greater T_H2-to-T_H1 cell ratio are more susceptible to viral infections, as the T_H1 response is crucial for limiting infections [28,35,50]. Deficiencies in T_H1 and IL-10 cytokines are associated with severe asthma exacerbations [33].

Inflammatory mechanisms other than the T_H2 pathway may also be involved. Rhinovirus infection activates IL-8 production, stimulating neutrophil release and bronchial hyperresponsiveness [51]. Neutrophils promote bronchial obstruction through release of elastase, leading to mucus production via neutrophil extracellular traps. Furthermore, defective eosinophilic inflammation in response to upper respiratory tract infections may increase susceptibility to asthma exacerbations [28,35,50].

Early viral infections in childhood may alter epithelial barrier integrity and functionality, alongside genetic and epigenetic mechanisms, thus increasing susceptibility to respiratory viruses in patients with asthma [44,52]. Experimental studies suggest that alarmin-induced ILC2 activation, which can be modulated by gut dysbiosis, may represent a common pathogenetic imprint in bronchiolitis caused by respiratory syncytial virus and subsequent recurrent wheezing. However, more exhaustive research in humans is required to determine how human ILC2s mediate the pathogenesis of wheezing and asthma.

Genetic Changes

Genetic changes also play a significant role in the programmed host response to infections. In recent years,

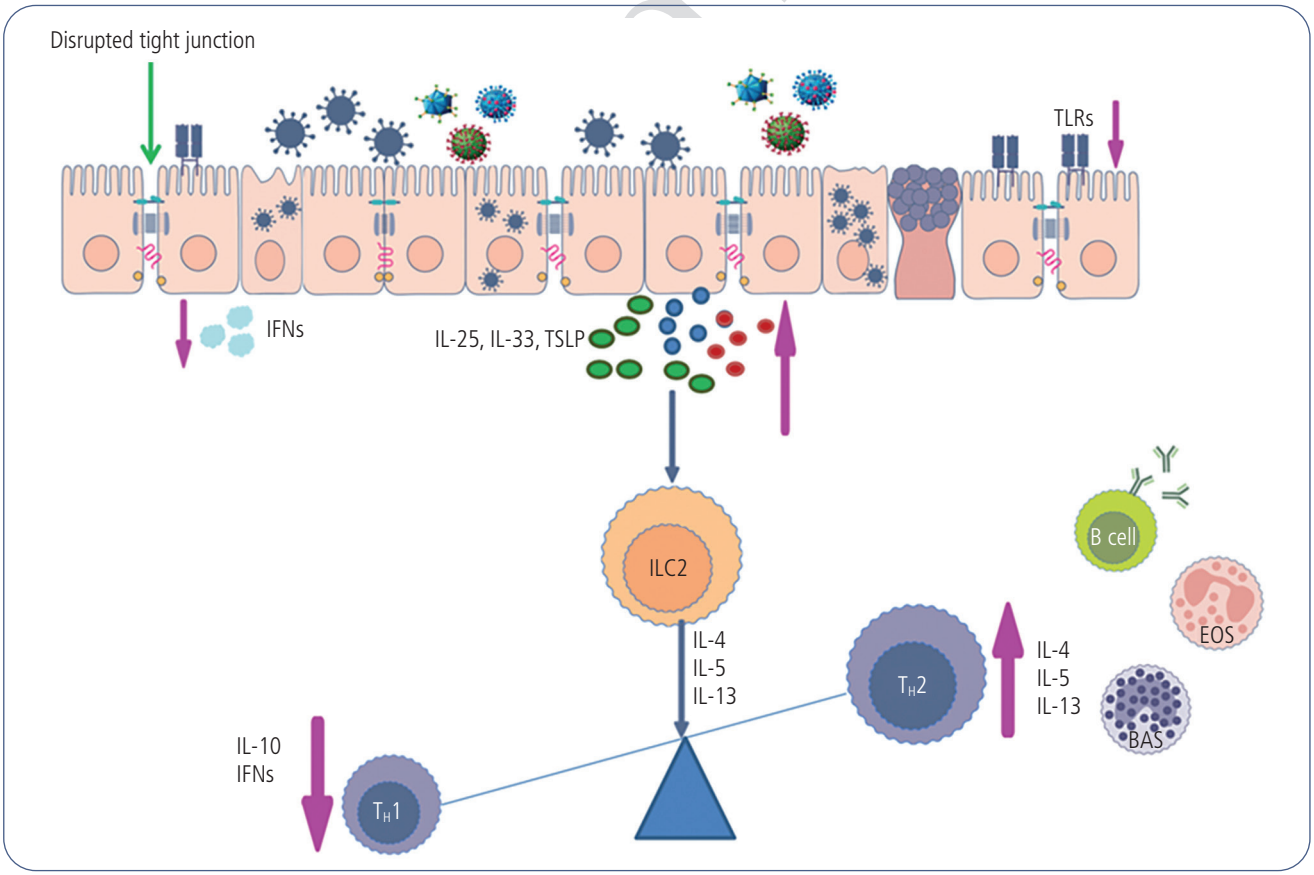

Figure 1. Altered epithelial and immune cell responses to viral infection in patients with asthma. IFN indicates interferon; TLR, toll-like receptor; IL, interleukin; TSLP, thymic stromal lymphopoietin; ILC, innate lymphoid cell; BAS, basophil; EOS, eosinophil.

many genetic polymorphisms relevant to both infection and asthma have been identified. Testing for the polymorphisms in the genes toll-like receptor 7 (*TLR7*) and *TLR8*, which recognize and respond to a variety of viruses, indicate that these are novel risk genes associated with asthma [53]. A key focus of polymorphisms has been detected in the locus of the transcription factor IRF1, which regulates IFN-γ production [54]. Additionally, a significant association has been identified between a polymorphism in the suppressor of cytokine signaling-1 (SOCS1) promoter and adult asthma, further emphasizing the role of genetic factors in antiviral responses [55].

In conclusion, bronchial epithelial cells in patients with asthma exhibit defective antiviral IFN production, releasing cytokines that stimulate T2-associated inflammation by ILC2s (Figure 1).

Inflammatory Profile of Asthma Exacerbations

Asthma is a biologically complex disease, with no pure T2 or T1 endotypes. This being the case, asthma exacerbations could also be expected to have a heterogeneous inflammatory nature. It is conceivable that the etiology of the exacerbations could determine the inflammatory pattern of the exacerbation, namely, infections would be associated with a T1 response and allergic/eosinophilic inflammation with a T2 response. Unfortunately, given the difficulty of performing techniques that could help to define the inflammatory pattern of an exacerbation (such as measurement of fractional exhaled nitric oxide [FeNO], sputum cytology, bronchoscopy), little information is available.

McDowell et al [56] conducted a study of 301 patients to assess, among other objectives, the stability of inflammatory phenotypes when stable and at exacerbation. Of note, no patients were receiving a biologic, and 38% were taking oral corticosteroids. $T2_{LOW}$ was defined according to FeNO values of ≤20 ppb and blood eosinophils <0.15×109/L, whereas $T2_{HIGH}$ was defined as FeNO of >20 ppb or blood eosinophils of >0.15×109/L. At least 1 exacerbation was recorded for 61% of the patents; of these, 65% were $T2_{HIGH}$. The study yielded 2 main findings. First, 26 of 71 patients (33%) produced spontaneous sputum. The pattern observed was neutrophilic in 26% (<2% eosinophils and ≥65% neutrophils), paucigranulocytic in 23% (<2% eosinophils and <65% neutrophils), mixed in 15% (>2% eosinophils and ≥65% neutrophils), and eosinophilic in 35% (>2% eosinophils and <65% neutrophils). Second, the phenotype at study entry was not significantly associated with the phenotype at exacerbation (P=.84; κ=0.12). Moreover, neither symptoms nor lung function enabled the inflammatory phenotype of the exacerbation to be distinguished, thus highlighting the need for additional tools beyond assessment of baseline characteristics.

Bjerregaard et al [57] classified 37 asthma exacerbations as eosinophilic (43%, defined as ≥3% sputum eosinophils) and noneosinophilic, finding that the prevalence of respiratory viruses was the same in eosinophilic and noneosinophilic exacerbations (44% vs 52%, P=.60), as was bacterial infection (6% vs 14%, P=.44). The relationship between infection and absence of eosinophils did not reach statistical significance, probably owing to the small sample size.

Wang et al [58] obtained sputum samples from a series of patients with asthma of different severity in the stable phase (29 adults and 49 children) and in exacerbation (22 adults and 29 children). In adult patients, there was a change in the cellular pattern from predominantly paucigranulocytic in the stable phase to eosinophilic in exacerbation. In children, however, a neutrophilic pattern predominated in exacerbation. The paucigranulocytic profile was infrequent in exacerbations, reflecting increased inflammation in these situations.

The inflammatory phenotype at steady state does not determine the inflammatory phenotype during exacerbation, which, in turn, is very heterogeneous and appears to be different in children and adults. Values may differ for patients receiving a biologic, as the biologic might significantly modify the inflammatory profile and the airway microbiota. The investigators of the MEX study recruited 145 patients who were receiving mepolizumab for a minimum of 3 months. Exacerbations were classified as sputum eosinophil $(SE)_{HIGH}$ (≥2% sputum eosinophils) or SE_{LOW} (≥2% sputum eosinophils) [59]. The exacerbations were SE_{HIGH} in 49% of cases and SE_{LOW} in 51%. The exacerbations were considered to be of infectious origin in 88% of SE_{LOW} and 40% of SE_{HIGH}. The inflammatory profile of exacerbations differed with the anti–IL-5 receptor, benralizumab. Poznanski et al [60] prospectively evaluated 104 severe corticosteroid-dependent patients who were prescribed benralizumab. Over a median treatment period of 14 months, only 2 exacerbations were associated with sputum eosinophilia, 16 were infective (based on intense neutrophilic sputum), and 2 had normal sputum (exacerbation associated with airway hyperresponsiveness). Therefore, it seems that the biologic drug specifically influences the inflammatory profile of exacerbations. The explanation may lie, at least in part, in changes in the microbiota induced by the biological treatment. However, Diver et al [61] did not find an increase in airway bacterial load or relative abundance of pathogenic organisms or a marked difference in microbial composition when subgroups with high or low sputum or blood eosinophils were compared. However, an elevated FeNO value indicated a subgroup with microbial profiles characterized by high α diversity and low relative abundance of Proteobacteria.

Therefore, further studies with biologics available in clinical practice—each case may well be different—are needed to identify the extent to which the inflammatory nature of exacerbations may be determined by changes in the microbiota or endotype.

Inflammatory Profile of Virus-Induced Asthma Exacerbations

As mentioned above, viral infections are responsible for most asthma exacerbations, and patients with asthma (especially those with severe forms of the disease) have defective immunity against viruses. As previously noted, viral infections are thought to trigger a T1 response in patients with asthma to promote viral clearance by the release of specific cytokines such as IFN-ϒ, IFN-β, and IFN-λ. In addition, early studies of bronchial inflammation in asthma attacks were based on autopsy findings, which revealed severe airway narrowing, mucus plugs, and neutrophil infiltration. These findings were corroborated in studies showing that

in patients intubated for an asthma attack, neutrophils were the dominant inflammatory leukocyte characterizing airway inflammation and that IL-8 was an important mediator of this neutrophilia [62]. Later studies found a dichotomy between time to death and the eosinophil/neutrophil ratio in cases of fatal asthma, with short-course fatal cases (<3 hours) being mainly neutrophilic and long-course fatal cases (>8 hours) being mainly eosinophilic [63].

Some published studies show that viral infection leads to bronchial neutrophilia. Zhu et al [64] investigated the bronchial mucosal inflammatory response in an experimental model of rhinovirus-induced asthma exacerbations, finding bronchial mucosal neutrophilia and more severe monocyte/macrophage infiltration in patients with asthma (10 patients) than in healthy individuals. Similar results were published by Jarjour et al [65] in 8 persons with a history of allergic asthma who were experimentally inoculated with rhinovirus strain (RV16): 96 hours after inoculation there was a significant increase in bronchial neutrophils compared with preinoculation values. This was accompanied by an increase in nasal concentrations of IL-8 and granulocyte colony-stimulating factor. Pizzichini et al [66] observed that natural colds (influenza A/B, rhinovirus, adenovirus, respiratory syncytial virus, and coronavirus infection) cause neutrophilic lower airway inflammation on day 4 that is more marked in patients with asthma than in healthy individuals. These findings were confirmed in 11 atopic patients with asthma and in 11 nonatopic healthy individuals: both groups developed significant increases in nasal neutrophils, IL-6, and IL-8 and modest increases in sputum neutrophils and IL-6, but not in IL-8, in response to viral infection [67].

As previously mentioned, the biology of asthma is complex, as is the virus-induced inflammatory response in patients with asthma. Fraenkel et al [68] conducted a study of experimental inoculation with RV16 using fiberoptic bronchial biopsy to examine the bronchial mucosa during rhinoviral infections in healthy individuals and patients with asthma. The authors observed an increase in epithelial eosinophils in patients who developed a cold; in patients with asthma, this appeared to persist into convalescence [68]. However, perhaps more important than the number of eosinophils is their degree of activation. In this sense, increased levels of eosinophil cationic protein were found in the sputum of RV16-infected atopic patients with asthma during the first week [69].

Altogether, these studies show primarily neutrophilic inflammation in response to viral infection, although this may be accompanied by eosinophilia in the airways of patients with asthma.

What Is the Mechanism of Action by Which Biologics Reduce Viral Exacerbations?

The increase in knowledge of the molecular mechanisms involved in asthma in general, and in severe asthma in particular, has changed the treatment paradigm in affected patients. While the cornerstone of treatment is based on inhaled corticosteroids throughout the severity spectrum, the recognition of specific therapeutic targets has facilitated the development of monoclonal antibodies, known as biologics, in severe refractory asthma [2,70].

As mentioned above, several authors have reported viral infections as the cause of >50% of asthma exacerbations [71]. In parallel, randomized controlled trials in severe asthma have repeatedly demonstrated biologic agents reducing moderate and severe asthma exacerbations by >50%. Therefore, it seems logical to infer that biological agents could decrease susceptibility to viral asthma exacerbations, possibly owing to the mechanism of action of biologics along the airway inflammatory cascade.

Efthimiou et al [72] speculated that T2 inhibitor therapies could have a dual mechanism regarding prevention and treatment in virus-induced exacerbations in severe asthma. Based on preclinical and clinical evidence, the authors postulate the existence of a beneficial counterregulation related to viral exacerbations and biologics. While T2 inhibitor drugs block cytokines involved in the airway inflammatory cascade, this inhibition could paradoxically upregulate the T1 response in charge of enhancing the INF response (Figure 2). The mechanisms underlying this counter-regulation remain to be fully elucidated, although these processes have recently been discussed [15]. Gill et al [73] reported that treatment with omalizumab restored the INF-α response to both rhinovirus and influenza in an in vitro pediatric asthma model. These results were significantly associated with a lower asthma exacerbation rate during the outcome period [74].

Sabogal-Piñeros et al [75] observed decreased macrophage, B-cell, and neutrophil values in rhinovirus-induced responses in patients with mild asthma treated with mepolizumab. SOCS-1 is a T2-inducible cytokine and a potent negative regulator of virus-induced IFN production; by reducing SOCS-1 levels, T2 inhibitors such as anti–IL-5, anti–IL-5R, anti–IL-4R, anti–IL-13, and anti-TSLP could increase IFN production by several key cells. In this context, blockade of SOCS-1 may act as one of the pivotal mechanisms underlying the beneficial counterregulation between T2 and T1 immune pathways by downregulating virus-induced asthma exacerbations [72].

In summary, the available evidence indicates that overexpression of T2 cytokines could be involved in a deficient response of T1 cytokines and INF, which are responsible for the natural antiviral response. The combination of overexpression of T2 cytokines and a viral respiratory infection would constitute the perfect storm for the development of an asthma exacerbation.

Importance of Characterizing Exacerbations in Clinical Practice

Recent studies attempting to characterize the inflammatory phenotype of asthma exacerbations have highlighted the utility of such an approach. In fact, as previously mentioned, patients with a T2-high or T2-low inflammatory asthma phenotype are at risk of presenting T2-high or T2-low exacerbations, irrespective of their baseline inflammatory phenotype. In parallel, and despite the evidence being scarce, the MEX study showed that 49% of exacerbations were eosinophilic under treatment with mepolizumab, whereas others reported that 10% of asthma exacerbations are eosinophilic under treatment with benralizumab [59,60]. Consequently, the authors suggest that, in contrast with patients receiving mepolizumab,

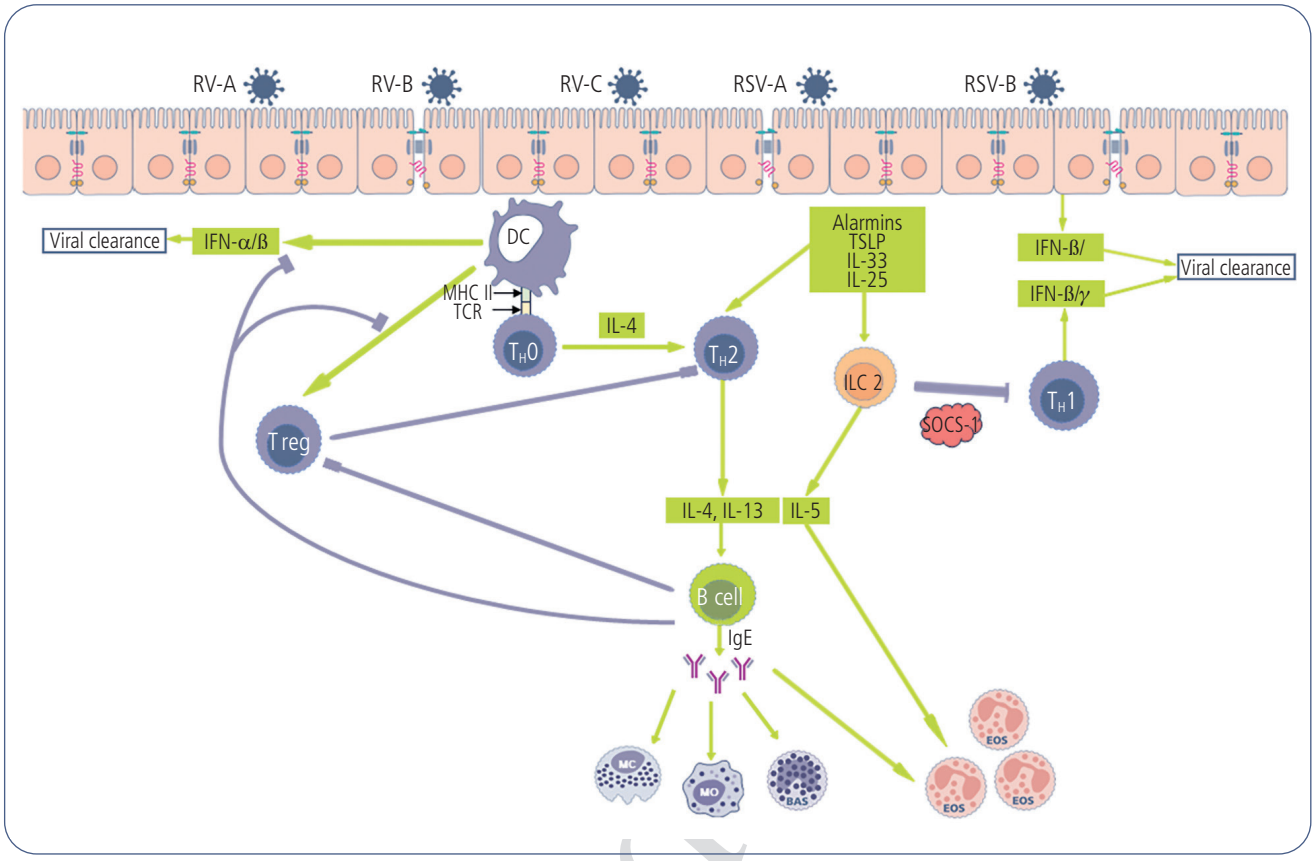

Figure 2. Epithelial and immune cell responses to viral infection in patients with asthma. Following infection, a wide range of mediators are secreted, leading to type 2 pathway upregulation through inflammatory mechanisms associated with T-helper type 2 (T_H2) and type 2 innate lymphoid cells (ILC2). Upregulation of the T_H1 immune pathway in response to the blockade of T2 cytokines is associated with increased interferon (INF). BAS indicates basophils; DC, dendritic cells; EOS, eosinophils; IL, interleukin; MC, mast cells; MO, macrophages; SOCS, suppressor of cytokine signaling; RSV, respiratory syncytial virus; RV, rhinovirus; T reg, T regulatory cells; TSLP, thymic stromal lymphopoietin. Green arrows, activation; blue arrows, inhibition.

patients receiving benralizumab do not present eosinophilic exacerbations owing to the drug's ability to penetrate lung tissue. In this context, they suggest treating T2-low and intensely sputum neutrophilic asthma exacerbations with antibiotics and propose switching the anti-T2 biologic if the patient presents T2-high asthma exacerbations despite treatment with a monoclonal antibody.

Similarly, exacerbations should be phenotyped in clinical practice, or at least an attempt to do so should be made whenever possible in severe asthma units, as this approach represents a step forward towards personalized decisions. If the exacerbations are bacterial, treatment with azithromycin or inhaled antibiotics might even obviate the need for a biologic. In patients already receiving biologics, T2 exacerbations might indicate an insufficient effect of the drug and point to the need for a switch [76].

Table 2 provides a checklist aimed at phenotyping exacerbations. This should be applied in daily practice in the subgroup of patients with severe asthma who are candidates for or are already receiving biological treatments. Some of the procedures are relatively simple, such as recording key information on probable triggers and performing blood analyses and microbiologic tests to identify the cause. These tests are widely available and are routinely performed in most emergency departments, and data can be recovered retrospectively, for instance, if the patients had to come to the hospital at night or during weekends.

The diagnosis of T2 exacerbations, on the other hand, is more complex. Few centers perform sputum induction in clinical practice, and the measurement of FeNO in an exacerbation is sometimes complicated, particularly in patients who are very tachypneic and/or require oxygen.

Sputum induction, if available, is very useful, although it is contraindicated if lung function is poor. Consequently, its use in moderate-severe exacerbations is limited. The MEX and Poznanski studies [59,60] only required that the patient had fluctuation of the usual symptoms, and that they call the research team to consult, thus making it easier for these studies to obtain sputum during exacerbations, although the scenario is different in most real-life settings. Spontaneous sputum for cytology and microbiological analyses and cultures remains an option in these cases. In this unfavorable scenario, some ongoing studies are attempting to discern the utility of FeNO or microbiological analyses to better understand the nature of asthma exacerbations [77,78].

More feasible biomarkers are needed to phenotype exacerbations in clinical practice (eg, via nasal cytology), as is evidence on the correlation with airway inflammation.

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Table 2. Checklist: Phenotyping Asthma Exacerbations in Patients With Severe Asthma.

Asthma endotype
Allergic, late-onset eosinophilic, AERD, overlap allergic/eos/AERD, ACOS
Biological
• … dose
• … start date
Immunotherapy
• … start date
Exacerbation details
Day 0: date …
Day of visit to the asthma HCP: …
Treatment before the visit to the HCP: …
Onset of exacerbation: rapid/slow … hours … days …
Environmental exposure (see also Table 1): pollen, molds, dust mites, pets
Occupational exposure … Other …
Vaccines received within the last week
NSAIDs intake: yes/no Which one / dose … Time until onset of symptoms …
Clinical manifestations
General: fever, malaise, myalgia, etc.
Lower respiratory symptoms: cough, wheezing dyspnea, chest tightness, chest pain, • Expectoration yes/no … • Color … • Quantity …
Upper respiratory symptoms: rhinorrhea, sneezing, naso-ocular itching, congestion, sore throat, watery/thick/color, nasal discharge
Physical examination
General
ENT
Pulmonary auscultation
SaO_2
Core Additional tests
Blood analysis: hemogram, CRP, ESR-minimum; according to the HCP's criteria – biochemistry, arterial gases, etc.
Plasma IL-6 (if available)
FeNO
Spirometry or PEF
PCR respiratory viruses: minimum influenza A and B, COVID, RSV, rhinovirus, …
Microbiology-bacteria-direct examination and cultures; mycobacterial cultures if indicated by HCP
Microscopic examination – sputum cellularity

Abbreviations: AERD, aspirin-exacerbated respiratory disease; ACOS, asthma–COPD overlap syndrome; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ENT, ear-nose-throat; SaO_2, oxygen saturation; HCP, health care professional; IL-6, interleukin 6; FeNO, nitric oxide exhaled fraction; PCR, polymerase chain reaction; PEF, peak expiratory flow; RSV, respiratory syncytial virus.

Conclusion

In conclusion, the need to phenotype asthma exacerbations for tailored management of patients with severe refractory asthma, particularly those undergoing biologic therapy, cannot be overstated. Identifying the underlying inflammatory profiles driving exacerbations is paramount if we are to optimize treatment strategies and improve patient outcomes. The dissociation between baseline inflammatory phenotypes and presentations of exacerbations underscores the necessity for individualized management paradigms. Utilizing sputum analysis to phenotype exacerbations provides invaluable insights into the predominant inflammatory pathways, guiding therapeutic decisions and potentially mitigating the burden of severe asthma exacerbations. Given the limited availability of sputum inflammation readings, particularly in the context of an exacerbation, other tools may help identify respiratory viruses, for example, blood eosinophil count, FeNO, C-reactive protein, and polymerase chain reaction with nasopharyngeal swabs. Furthermore, distinct responses to biologic therapies highlight the importance of phenotyping exacerbations in refining treatment algorithms and maximizing therapeutic efficacy. Hence, embracing phenotyping as a standard practice is pivotal for advancing the management of severe asthma and enhancing patient care in the realm of precision medicine.

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Conflicts of Interest

In the last 3 years, IO declares having received honoraria for participating as a speaker in meetings sponsored by AstraZeneca, Boehringer-Ingelheim, Chiesi, and Novartis and as a consultant for AstraZeneca, GlaxoSmithKlein, Puretech, and Sanofi. He has received financial aid from AstraZeneca, Bial, and Chiesi for attending congresses and grants from Sanofi for research projects. SQ has been on advisory boards for and has received speaker's honoraria from Allergy Therapeutics, AstraZeneca, GlaxoSmithKline, Novartis, Chiesi, Gebro, and Sanofi. IB is a member of national or international

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