Asthma-associated bacterial infections: Are they protective or deleterious?

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Eosinophilic, noneosinophilic, or mixed granulocytic inflammations are the hallmarks of asthma heterogeneity. Depending on the priming of lung immune and structural cells, subjects with asthma might generate immune responses that are T_H2-prone or T_H17-prone immune response. Bacterial infections caused by *Haemophilus*, *Moraxella*, or *Streptococcus* spp. induce the secretion of IL-17, which in turn recruit neutrophils into the airways. Clinical studies and experimental models of asthma indicated that neutrophil infiltration induces a specific phenotype of asthma, characterized by an impaired response to corticosteroid treatment. The understanding of pathways that regulate the T_H17-neutrophils axis is critical to delineate and develop host-directed therapies that might control asthma and its exacerbation episodes that course with infectious comorbidities. In this review, we outline clinical and experimental studies on the role of airway epithelial cells, S100A9, and high mobility group box 1, which act in concert with the IL-17-neutrophil axis activated by bacterial infections, and are related with asthma that is difficult to treat. Furthermore, we report critically our view in the light of these findings in an attempt to stimulate further investigations and development of immunotherapies for the control of severe asthma. (J Allergy Clin Immunol Global 2023;2:14-22.)

Key words: *Severe asthma, bacterial infections, neutrophil, IL-17, lung inflammation*

Abbreviations used

AEC: Airway epithelial cell
AHR: Airway hyperresponsiveness
CCL: Chemokine (C-C motif) ligand
DC: Dendritic cell
HDM: House dust mite
HMGB1: High mobility group box 1
NE: Neutrophil elastase
NET: Neutrophil extracellular trap
NF-kB: Nuclear factor kappa B
OVA: Ovalbumin
PRR: Pattern recognition receptors
TLR: Toll-like receptor
Treg: Regulatory T

Asthma is a chronic disease characterized by airway inflammation, reversible or irreversible airway obstruction, airway hyperresponsiveness (AHR), and lung remodeling. Coughing, wheezing, shortness of breath, and chest tightness are the symptoms of the disease.[1,2] Asthma is viewed as a complex and heterogeneous syndrome, which phenotypically may be classified as mild, moderate, and difficult to treat to severe, that is most likely caused by a combination of genetic predisposition, changes in lifestyle, and environmental factors. Despite this heterogeneity and complexity, 2 endotypes of asthma are defined: allergic (or atopic) and nonallergic asthma.[3]

Asthma affects children, teenagers, and adults. According to the Global Asthma Network, 339 million people are affected worldwide.[4,5] The prevalence and mortality associated with asthma changes from one region to another. Indeed, although the prevalence of asthma is elevated in high-income countries, the highest number of deaths is recorded in low- and middle-income countries, which corresponds to more than 80% of asthma-related deaths.[2,6] The global prevalence of asthma also depends on sex and age. The incidence and prevalence of asthma are higher in children, but its morbidity and mortality are higher in adults. Sex prevalence varies along life, with higher prevalence among boys than among girls. However, for all adulthood, females are more affected than males.[5]

In this review, we will address current knowledge about the mechanisms that modulate neutrophilic inflammation in a specific asthma phenotype, which is difficult to treat, in the context of bacterial infectious comorbidities in an attempt to highlight the challenges and to overcome them for the development of host-directed therapies.

PATHOGENESIS OF ASTHMA

Allergic asthma is defined by eosinophilic infiltrate, mast cell activation, and IgE production.[7] Usually, allergic asthma has an

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early onset and is associated with other allergic conditions such as allergic rhinitis and atopic dermatitis.[3] Nonallergic asthma has a late onset and might be characterized by a T_H2-high immune response with eosinophilic infiltrate, or T_H2-low immune response. T_H2-low endotype is characterized by neutrophilic inflammation that could be due to obesity, environmental exposure to pollutants such as diesel particles and cigarette smoke, or infections.[3,8,9]

In T_H2-high asthma, eosinophilic inflammation is one of the main readouts of the disease. Allergens are recognized by PRRs, including Toll-like receptor (TLR)-4, on airway epithelial cells (AECs) and stimulate the secretion of IL-25, IL-33, thymic stromal lymphopoetin, GM-CSF, IL-1, chemokine (C-C motif) ligand (CCL)2, CCL20, and β-defensins. AECs also release ATP, lysophosphatidic acid, uric acid, and reactive oxygen species. Cytokines and chemokines recruit and activate dendritic cells (DCs) and type 2 innate lymphoid cells, which secrete IL-5, IL-9, and IL-13 and stimulate the differentiation of T_H2 cells. T_H2 cells secrete IL-4, IL-5, and IL-13 and induce allergen-specific IgE production.[7,10] IgE binds to high-affinity IgE receptor on mast cells. Subsequent contacts with the allergen induce mast cell degranulation and immediate allergic reaction mediated by histamine, cysteinyl leukotrienes, and cytokines as tumor necrosis factor.[11] T_H2 cells, eosinophils, and basophils induce late allergic reaction. Although memory T_H2 cells recognize antigens that usually are innocuous to the host and mediate eosinophil differentiation and recruitment, and collaborate for mucus production, eosinophils and basophils play a role in the induction of tissue damage mediated by major basic protein, eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin.[12]

The identification of additional T_H-cell subsets brought new insight about the complexity of asthma pathogenesis. Higher number of circulating T_H9 cells and increased levels of IL-9 were detected in allergic asthmatic patients compared with nonallergic subjects and in the asthma murine model.[13-15]

T_H17 cells also participate in the immunopathology of asthma. Although IL-17 is associated with neutrophilic asthma, high levels of IL-17 in the airways and increased levels of IL-22 in the serum of patients with asthma compared with healthy individuals suggested that these cytokines also participate in the immune response of allergic asthma.[16-19] Fig 1 summarizes the description of immunopathology in the allergic asthma.

The heterogeneity of asthma endotypes includes eosinophilic (allergic and nonallergic), noneosinophilic (neutrophilic, T_H1/T_H17, and paucigranulocytic), and mixed granulocytic inflammation.[20] Subjects with asthma might generate a T_H2-prone and/or T_H17-prone immune response depending on the inflammatory milieu. The persistent neutrophilic inflammation, which might be complete or partially mediated by T_H17 cells, or mixed eosinophilic/neutrophilic inflammation has been reported as severe asthma.[21,22] Subjects with neutrophilic airway inflammation were refractory to inhaled corticosteroid treatment.[23]

High levels of IL-17 in serum[19] and in the lung[16,24] were reported in allergic asthmatic patients, but few clinical studies involving T_H17-related cytokines (IL-17, IL-23, and IL-22) were performed. In a randomized, double-blind, placebo-controlled study, the blocking of IL-17 signaling using brodalumab (anti–IL-17RA mAb) in subjects with inadequately controlled moderate to severe asthma had no evidence of an effect in the overall study population; however, an increase in symptom-free days was observed in the high-reversibility subgroup treated with brodalumab, encouraging further study of IL-17 blockade in this asthma subgroup.[25] Concerning IL-23 signaling, a recent data of a randomized, phase 2a, multicenter, and double-blind clinical trial with risankizumab (anti–IL-23p19 mAb) showed that the treatment was not beneficial in severe asthma.[26] Although anti–IL-22 therapies have not been evaluated in asthma yet,[27] the use of fezakinumab (anti–IL-22 mAb) was efficient in severe atopic dermatitis, which has similar inflammatory features of asthma.[28] A metadata study showed that a subset of subjects with asthma may respond to anti–IL-22 antibody therapy.[29] Nevertheless, a deeper investigation is needed to ascertain the role of IL-17 and IL-22 in the modulation of T_H2 immune responses. Considering that IL-22 activates DCs,[30,31] it will be relevant to investigate whether IL-22 plays a direct or an indirect role in other innate cells, such as eosinophils. Interestingly, the presence of IL-22 was detrimental during the sensitization phase, but it was protective during the allergen challenge,[18] suggesting a time-dependent effect of IL-22.

In moderate to severe asthma, AECs secrete neutrophil chemoattractant CXCL8 (IL-8), CCL2, and CCL20, which recruit DCs.[32] Activated DCs migrate to the mediastinal lymph node where they prime naive T cells to differentiate into T_H17 cells through the expression of IL-1β, TGF-β, IL-6, and IL-23 by DCs. Primed T_H17 cells migrate into the lungs and produce IL-17 and IL-22.[22] T_H17 cells increase mucus production (IL-17) and exacerbate AR (IL-17/IL-22) in severe asthma.[33] In addition, IL-17 directly acts on bronchial smooth muscle contraction through the upregulation of Ras homolog family member A protein, associated with actomyosin contractility.[34] During severe asthma, type 3 innate lymphoid cells are early providers of IL-17 and IL-22. Type 3 innate lymphoid cells may play a critical role in severe asthma phenotypes by producing IL-17 and IFN-γ, which stimulate neutrophil recruitment,[10] besides IL-22. IL-17 sustains neutrophilic inflammation by stimulating CXCL1 and CXCL8 production by AECs. CXCL1 and CXCL8 enhance airway smooth muscle contraction and stimulate collagen synthesis.[21,35] Furthermore, T_H17 cells and IL-17 induce the expression of polymeric immunoglobulin receptor in the airway epithelium and a subsequent increase in airway IgM and IgA levels in mice.[36] Therefore, IL-17 plays a key role in the mucosal immune response by regulating IgA production and transport to the lungs and gut.[36-38] This pathway if unbalanced might be deleterious to the host and cause pathology.

IL-22 enhances airway smooth muscle contraction, promotes collagen deposition and production of S100A9, an alarmin that induces neutrophil influx, by AECs, and is associated with neutrophil survival by inhibiting apoptosis pathway. S100A9 may stimulate AECs to produce neutrophil survival cytokines such as MCP-1, IL-6, and CXCL8.[39-42] Increased levels of S100A9 were reported in the sputum of subjects with severe uncontrolled asthma compared with subjects with controlled asthma,[43] suggesting that S100A9 could be a biomarker of neutrophilic inflammation in severe asthma.[43,44] In an animal model of neutrophil-dominant asthma generated using ovalbumin (OVA) and complete Freund's adjuvant, S100A9 was reported to generate and amplify neutrophilic inflammation followed by a high production of IL-1β, IL-17, and IFN-γ in the lungs lysates.[44] S100A9 interacts with TLR4 or receptor for advanced glycation end products in granulocytes and induces its own production in these cells. S100A9 may also interact with TLR4 or receptor

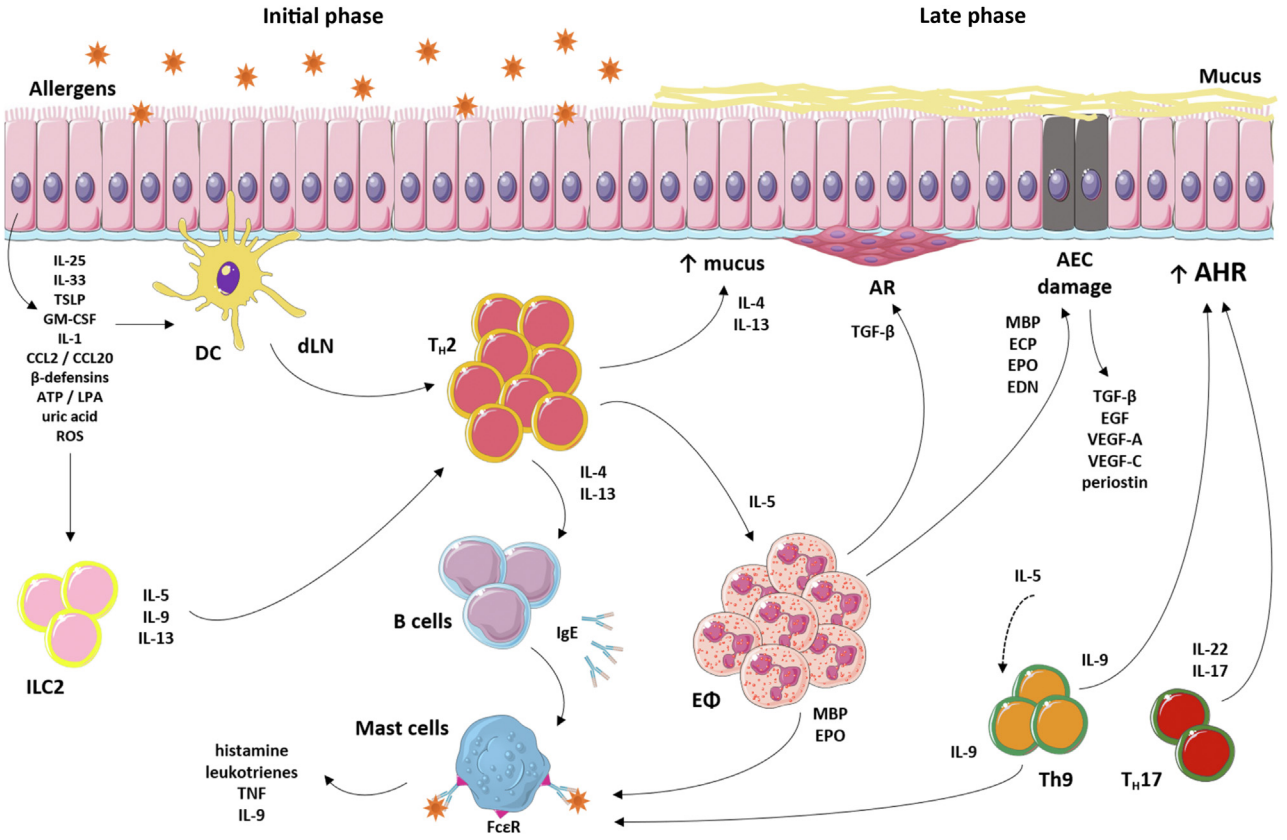

FIG 1. Immunopathology of allergic asthma. Inhaled allergens activate AECs that recruit and activate DCs and ILC2s by production of IL-25, IL-33, TSLP, ATP, uric acid, LPA, and ROS. DCs and ILC2s induce T_H2 differentiation and activation. T_H9 and T_H17 might also undergo differentiation. Eosinophil (EΦ) recruitment and activation followed by activation of T_H2, T_H9, and T_H17 promote AHR and mucus production, AEC damage, and AHR. *ILC2*, Type 2 innate lymphoid cell; *LPA*, lysophosphatidic acid; *ROS*, reactive oxygen species; *TSLP*, thymic stromal lymphopoetin.

for advanced glycation end products in monocytes. In both cells, S100A9 induces the production of IL-1β, IL-6, IL-18, and tumor necrosis factor. IL-1β has an autocrine and paracrine effect on both granulocytes and monocytes.[45]

In severe asthma, S100A8 and S100A9 induce also the production of high mobility group box 1 (HMGB1), a proinflammatory alarmin produced by inflammatory and airway cells.[46] Sputum levels of HMGB1 were significantly higher in children with severe asthma compared with children with mild and moderate asthma.[47] In addition, in a model of neutrophilic asthma induced by OVA combined with LPS, anti–HMGB1-neutralizing antibody administered intranasally before OVA sensitization reduced neutrophilic inflammation, IL-17 production, and AHR.[48] As S100A9, HMGB1 also interacts with receptor for advanced glycation end products and TLR4 and induces the release of neutrophil extracellular traps (NETs).[49,50] NETs play a detrimental effect because their compounds histones, neutrophil elastase (NE), myeloperoxidase, cathepsin G, and DNA cause tissue damage.[51]

The role of NETs in severe asthma is not limited to tissue damage in AECs. NETs might indirectly stimulate the recruitment of neutrophils into the airways by a mechanism dependent on NET-activated AECs, which secrete CXCL1, CXCL2, and CXCL8 and drive neutrophilic inflammation through the TLR4/nuclear factor kappa B (NF-kB) pathway.[52] Likewise, another study showed that during severe asthma, NETs induce a second wave of neutrophil infiltration in the airway by stimulating macrophages to produce IL-1β, which intensifies the recruitment of neutrophils and the production of NETs. The accumulation of NETs may amplify tissue damage and aggravate asthma pathology.[53] Activated neutrophils produce reactive oxygen species, antimicrobial peptides, elastase, and matrix metalloproteinase-9.[54,55] Reactive oxygen species, NE, and matrix metalloproteinase-9 may be involved in tissue damage during severe asthma.[56] NE augments CXCL8 production by AECs, promoting a loop in neutrophil recruitment as well as the inactivation of tissue inhibitor of metalloproteinase-1. Increased levels of matrix metalloproteinase-9 and NE and decreased levels of tissue inhibitor of metalloproteinase-1 contribute to bronchoconstriction in asthma.[57] Fig 2 summarizes the description of immunopathology in severe asthma.

ASTHMA AND INFECTIOUS COMORBIDITIES

Viral, bacterial, and fungal infections might accelerate the progression of asthma and induce severe disease.[57] Therefore, the therapeutic management of asthma is more difficult during infectious comorbidities. The relationship between asthma and infections is complex and involves the pathogen and factors associated with the host genetic background. Overall, the failure in mechanisms of pathogen tolerance induces host cell death and might cause tissue injury. The recognition of microbial-

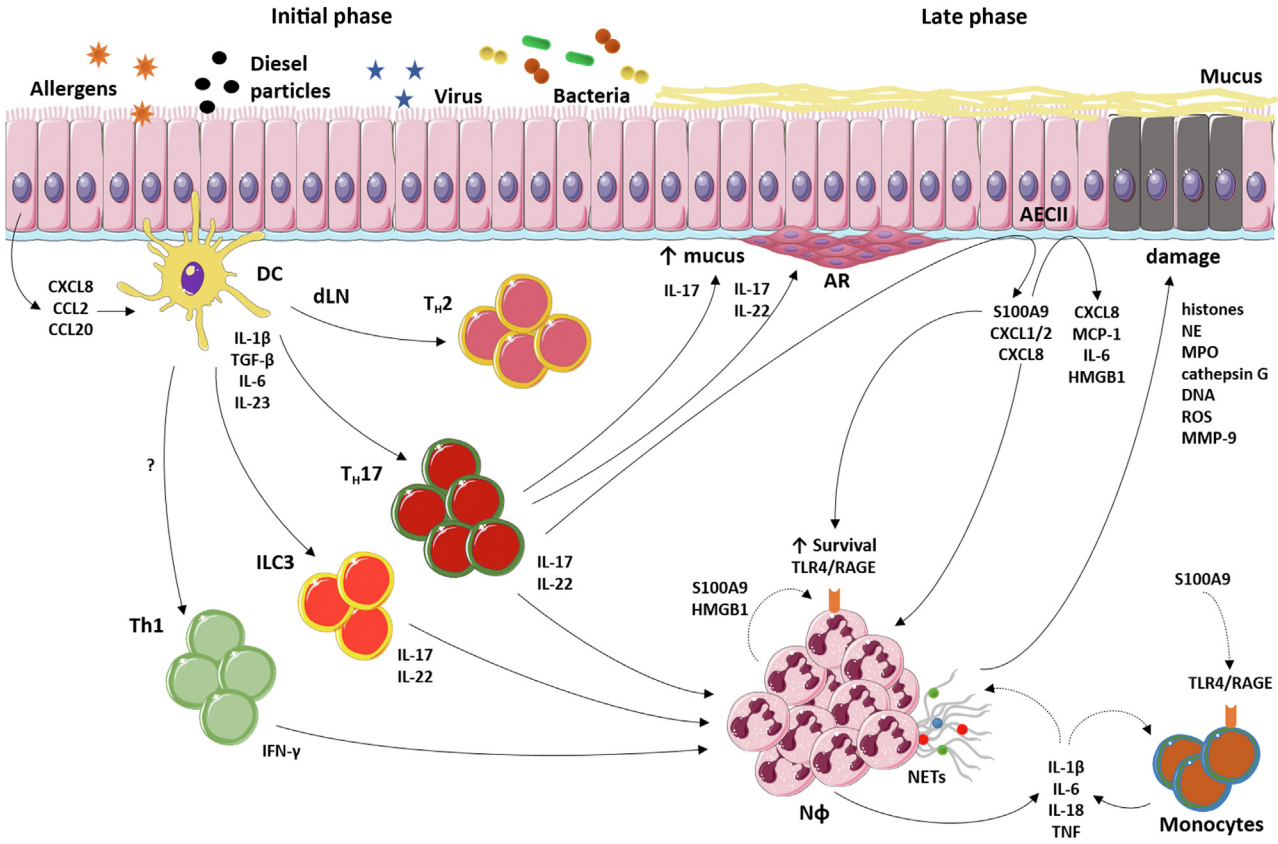

FIG 2. Immunopathology of severe asthma. Allergens, pollutants, and viral/bacterial infections promote the activation of AECs that recruit and activate DCs by production of IL-1β, IL-6, CXCL8, CCL2, and CCL20. DCs migrate to draining lymph node (dLN) and induce T_H1, T_H2, and T_H17 cell differentiation. ILC3s provide the early sources of IL-17 and IL-22. ILC3, T_H17, and T_H1 contribute to recruit neutrophils (NΦ). NΦ cause epithelial damage by release of NETs. AEC-derived signals (S100A9, CXCL1, CXCL2, and CXCL8) stimulate the NΦ survival and recruitment, respectively. The interface of neutrophils and AECs amplifies the local inflammation and aggravates asthma immunopathology. *ILC3*, Type 3 innate lymphoid cell.

associated molecular patterns by pattern recognition receptors on host cells activates innate leukocytes that secrete proinflammatory cytokines and regulate positively the expression of MHC and costimulatory and adhesion molecules. Signaling through cytokines and PRRs drives the differentiation of $CD4^+$ T-cell subsets. This is the critical outcome in the landscape of comorbidities that might affect the type and magnitude of inflammation in subjects with asthma. Although the immune response and inflammatory response against the infection is important for pathogen control, they may worsen the episodes of asthma and cause severe disease. The comprehension of the mechanisms by which microbial components are detrimental or protective in asthma might provide the basis for host-directed therapies for severe asthma. In this sense, 2 detrimental possibilities may be considered in asthma and infection comorbidities: (1) asthma impairs and weakens the immune response against pathogens and (2) infections change asthma phenotype and induce a difficult-to-treat or severe asthma endotype.

It should be noticed that in opposition to this notion, the hygiene hypothesis elegantly explored and supported the idea that infections might negatively regulate type 2 inflammation, the hallmark of allergic asthma. The hygiene hypothesis might be briefly summarized by stating that the exposure to pathogens, or infectious agents or their molecules, drives the immune response to the T_H1 profile or toward regulatory T (Treg) cells, and counteracts or reduces the T_H2 profile.[58] In the former decade, we evaluated the therapeutic potential of experimental vaccines against tuberculosis in an asthma model. Subunit vaccines and a DNA vaccine with mycobacterial antigens, used as allergen-free immunotherapies in murine asthma model with OVA or *Dermatophagoides pteronyssinus* protein (Der-p1), reduced airway inflammation and improved pulmonary function.[59-62]

Although infections might regulate diversely the immunopathology of asthma, in the following section, we shall discuss how the infections drive the severity of asthma and we will focus on how airway and pulmonary bacterial infections might be detrimental in asthma. This field deserves investigations to advance in the search of targets for immunotherapies. Furthermore, in our critical view, the order of stimuli (allergen-infection or infection-allergen) and the time-dependency of infection are critical factors that drive the exacerbation or reduction of asthma immunopathology.

BACTERIAL INFECTIONS AND ASTHMA EXACERBATIONS

Pathogenic bacteria, atypical bacteria, and lung microbiota might affect the immunopathology of asthma.[20,22,63-66] The

association between atypical bacteria, as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, and asthma exacerbation is strongly associated with the enhancement of allergic asthma phenotype and type 2 inflammation induced by the infection.[64]

Clinical evidence and experimental studies support a significant association between asthma severity and changes in bacterial community profiles. A recent clinical trial with 214 children showed alterations in the airway microbiota at time of early loss of asthma control. The airway microbiota dominated by *Corynebacterium* and *Dolosigranulum* was associated with favorable clinical outcomes compared with microbiota dominated by pathogenic bacteria, including *Staphylococcus*, *Streptococcus*, and *Moraxella*.[67] These data reinforce the results obtained in a study with adults classified as adults with mild asthma, which revealed a negative correlation between the relative abundance of *Corynebacterium* and *Moraxella* in nasal brush. In addition, this study showed that the relative abundance of *Moraxella* and *Streptococcus* correlated positively with systemic eosinophilia and lower airway eosinophils and bronchial levels of tumor necrosis factor and IL-7, respectively.[68] In 17 of 28 treatment-resistant patients with severe asthma, the dominant species within the airway bacterial community were *Moraxella catarrhalis* and members of *Haemophilus* and *Streptococcus* genera. Chronic infections with these species were associated with longer asthma duration and positively correlated with higher IL-8 concentrations and neutrophil counts in the sputum.[69] If there is such relationship, further studies are necessary to indicate which one comes first, asthma severity or bacterial chronic infections.

Chronic bacterial infections are possible factors that contribute to the development of neutrophilic asthma[20,22] and the neutrophil-mediated inflammation could explain the inefficacy of corticosteroids in a T_H2-low asthma phenotype.[20] Considering this, antibiotic therapy has been suggested. Treatment with macrolide (azithromycin) as an immunomodulator and anti-inflammatory agent for 6 months reduced the exacerbation in those with noneosinophilic asthma, suggesting that chronic bacterial infections in T_H2-low patients is a significant contributing factor to exacerbation risk.[70]

Airway neutrophils from subjects with asthma spontaneously release lower levels of IL-8, IL-1β, and tumor necrosis factor compared with healthy controls, suggesting an impaired role of these cells, which may impact the susceptibility to airway infections.[71] Both bacteria from *Haemophilus* and *Streptococcus* genera require neutrophils to control chronic infections,[72,73] and the function of neutrophils is compromised in asthma milieu.

Haemophilus influenzae

H influenzae is a Gram-negative, nonencapsulated bacterium that chronically infects the airways and is the most common isolated bacteria from patients with asthma, associated with neutrophilic asthma and corticosteroid-reduced response in asthma.[74] Accordingly, abundance of *H influenzae* in the airways is associated with predominance of neutrophils in the sputum of patients with asthma.[75]

The cell type mostly infected by *H influenzae* is AECs. Nontypeable *H influenzae* is recognized in the airways by TLR2, resulting in Myd88 recruitment with NF-κB activation. However, the subsequent effector mechanisms responsible for the clearing of the infection and the control of inflammatory response remain elusive.[76] Mice previously infected with *H influenzae* and submitted to OVA-induced asthma exhibited a higher bacterial load compared with single infected mice. Furthermore, chronic *H influenzae* infection and OVA exposure induced neutrophilic inflammation and T_H17 responses that promoted bacterial persistence, leading to the development of a phenotype similar to steroid-resistant neutrophilic asthma.[77] Anti–IL-17 treatment of OVA-sensitized and *H influenza*–infected mice completely inhibited airway neutrophilic inflammation induced by the infection, suggesting that neutrophilic inflammation is dependent on IL-17.[73] In addition, infection by nontypeable *H influenzae* in mice exposed to allergen promotes increase of AHR, MUC5A, and MUC5B expression and is associated with hyperphosphorylation of p38 mitogen-activated protein kinase. The combined treatment with dexamethasone and SB203580, a specific inhibitor of p38, substantially suppressed the *H influenzae*–induced asthma exacerbation.[78] On the basis of these findings, the authors suggested that cotreatment with dexamethasone and SB203580 could be a novel strategy against steroid-resistant asthma.

Acute *H influenzae* infection induces T_H17 cells, neutrophil influx, increased mucus production, and attenuation of the lung function in mice.[79] Long-term exposure to low dose of *H influenzae* after OVA challenge resulted in increased tissue remodeling and reduced number of Treg cells in the lungs and IL-10 levels in the bronchoalveolar lavage fluid, suggesting an impaired anti-inflammatory response during the comorbidity.[79]

In a recent randomized clinical trial, azithromycin treatment for 48 weeks of adults with uncontrolled asthma reduced *H influenzae* load in sputum and efficiently reduced the asthma exacerbations rate.[80] However, this long-term treatment favored the antibiotic resistance to *Staphylococcus aureus*, but not to *H influenza* and *S pneumoniae*. These findings show that the comorbidity asthma and bacterial infections must be treated in 2 ways: short-term antibiotic and regulation of inflammatory response. Therefore, the search for new anti-inflammatory targets to control bacterial infection–associated asthma exacerbations is critical.

Moraxella catarrhalis

M catarrhalis is a Gram-negative diplococcus, nonencapsulated bacterium that colonizes the mucosal membranes of nasopharynx. *M catarrhalis* has emerged as a transmittable pathogen, causing infections such as pneumonia, laryngitis, endocarditis, meningitis, and otitis media.[81] Particularity, *M catarrhalis* is associated with chronic obstructive pulmonary disease and asthma exacerbations. Bacteriome characterization of hospitalized children with asthma in consequence of an episode of asthma exacerbation showed the presence of *M catarrhalis* in the nasopharyngeal swabs.[82] Moreover, children with asthma with nasal airway microbiota colonized predominantly by *Moraxella* genera have an increased risk of asthma exacerbations.[83]

Epithelial cells from mucosal surface are the main targets of *M catarrhalis*. In the alveoli, *M catarrhalis* interacts with TLR2, TLR4, and TLR9 from AECs, resulting in NF-κB activation. Consequently, AECs increase the expression of adhesion molecules (intercellular adhesion molecule 1 and vascular cell adhesion molecule 1), and produce CCL2 and MCP-1, which recruit monocytes and DCs.[81] Lipooligosaccharidae from the bacterial membrane activates TLR4 in macrophages by a mechanism dependent on CD14, leading to NF-κB activation and production of IL-6, IL-8, and tumor necrosis factor.[84] IL-6, tumor necrosis

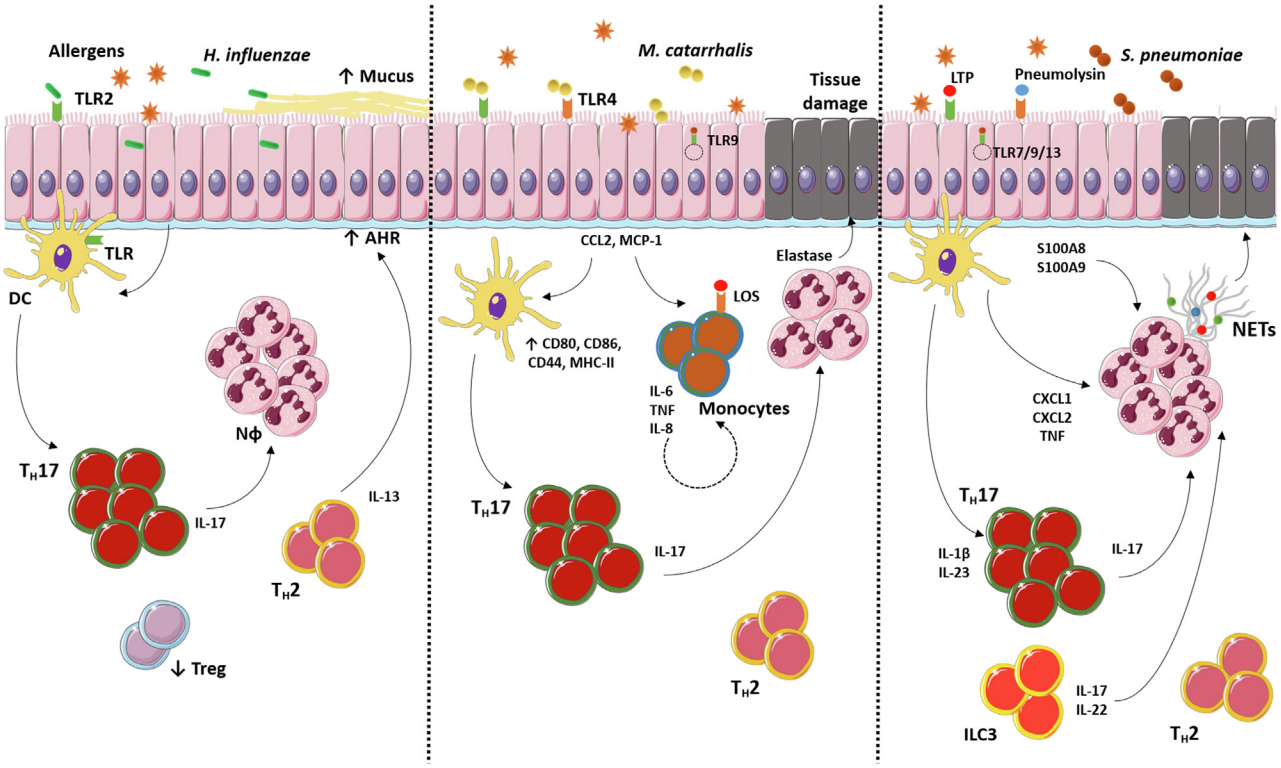

FIG 3. Bacterial infections and asthma exacerbation. Bacterial infections activate TLRs on DCs and might drive the allergic immune response from T_H2 to T_H2/T_H17 cells. Activated eosinophils and neutrophils produce inflammatory mediators that activate smooth muscle cells and damage epithelial cells, which release S100A8 and S100A9 alarmins. T_H17 cells might indirectly aggravate the immunopathology of asthma, inducing the recruitment of neutrophils that produce NETs.

factor, and IL-8 produced by macrophages result in recruitment and activation of monocytes, and exacerbation of inflammatory response.[81,85] The recognition of pathogens by DCs results in an increase in costimulatory molecules (CD80 and CD86), CD44, an adhesion molecule, and MHC-II expression. In addition, activated DC promotes both $CD8^+$ and $CD4^+$ T-lymphocyte activation.[81] $CD4^+$ lymphocytes secrete cytokines that induce recruitment and activation of granulocytes. As a consequence, activated neutrophils release elastase, which induces tissue damage.

Asthma exacerbations caused by *M catarrhalis* infection are also associated with recruitment and activation of T_H17 cells. In a mouse model of HDM-induced asthma, *M catarrhalis* infection in different time points of allergic airway inflammation induced severe airway inflammation and mucus production and added to increased concentrations of IL-17 and neutrophils in the bronchoalveolar lavage fluid.[86] IL-17 knockout mice exposed to allergen and infected displayed a significant reduction in neutrophils in the bronchoalveolar lavage fluid, in the lung inflammation, and in mucus production, indicating that IL-17–producing $CD4^+$ cells were a key mediator of *M catarrhalis*–induced asthma exacerbations.[86]

Streptococcus pneumoniae

S pneumoniae is a Gram-positive diplococcus bacterium that frequently colonizes the human nasopharynx. Pneumococcal infections lead to serious invasive diseases such as meningitis, septicemia, and pneumonia, and are an important cause of morbidity and mortality among children and in older adults.[87,88]

The susceptibility to *Streptococcus* infection was already described in patients with asthma. A study with 224 patients with asthma and 668 males without asthma showed that asthma was the only significant risk factor for *S pneumoniae* carriage.[89] A nested case-control study conducted with 635 subjects with invasive pneumococcal disease and 6350 controls showed that subjects with asthma had an increased risk of invasive pneumococcal disease.[90]

In the alveoli, *S pneumoniae* interacts with type II AECs, alveolar macrophages, and DCs through the recognition of pathogen-associated molecular patterns (PAMPs) by PRRs; pneumococcal lipoteichoic acid and cell wall peptidoglycanas are recognized by TLR2, pneumolysin is recognized by TLR4, and CpG motifs are recognized by TLR9.[91] An important synergy among TLRs has been described in response to *S pneumoniae*, especially TLR2/4/9 for induction of cytokines and chemokines[92] and TLR7/9/13 associated with susceptibility to infection.[93] TLR activation induces the production of tumor necrosis factor, CXCL1, and CXCL2, which recruit neutrophils. AEC also release alarmins, as S100A8 and S100A9, in the early phase of *S pneumoniae* infection that precedes neutrophil recruitment.[94] Although the activation of individual TLRs has a limited role in pneumococcal infection, MyD88, the adaptor protein of the signaling pathway of TLR, is crucial for initiating proinflammatory cytokine release and for the enhanced production of antimicrobial peptide to restrict *S pneumoniae* outgrowth.[95] DC recognize and phagocyte

pneumococcal mainly by pneumococcal adherence and virulence factor A and release IL-1β, IL-6, IL-8, IL-12, and tumor necrosis factor.[96] Airway DC, specially $CD103^+$ subset, might induce the release of IFN-γ and IL-17 by invariant natural killer cells,[97] whereas it has been shown that bone marrow–derived DC are important to induce T_H17-adaptive immune response,[98,99] both important to pneumococcal clearance. During pneumococcal infection, T_H17, T_H1, and T_H2 cells are critical to clear *S pneumoniae* infection. T_H1 and T_H17 cells recruit and activate macrophages and neutrophils, and T_H2 cells release IL-4 and induce the production of antibodies.[72] A potential synergistic effect of T_H17 cells and antibodies induces, respectively, increased recruitment of neutrophils and opsonization, which improve the control of chronic bacterial infection.[100] Besides antimicrobial defense mechanisms, neutrophils use NETs to restrict bacterial spreading.[101] Furthermore, IL-17 amplifies type II AEC activation by increasing the production of antimicrobial peptides and chemokines.[102] IL-17 and IL-22 are also produced by type 3 innate lymphoid cells by a mechanism dependent on DC, IL-1β, and IL-23.[41,103,104]

Although the susceptibility to *S pneumoniae* infection is increased in patients with asthma, the effect of infection during asthma episodes is still controversial and needs to be clarified. The induction of T_H1, T_H2, and T_H17 cells and the recruitment of neutrophils are potential risks for the development of severe asthma, and as we discussed previously, the exacerbation of pulmonary inflammation generates tissue damage.

Epidemiological and experimental findings showed a protective role for *S pneumoniae* infection in asthma. Children with asthma treated with sulfisoxazole and pneumococcal vaccine showed 56% reduction in the frequency of acute asthmatic attacks and 90% decrease in hospitalizations associated with otitis media.[105] Similarly, a retrospective cohort study, which evaluated the effectiveness of a 23-valent pneumococcal polysaccharide vaccine, showed that the vaccination decreased the risk of hospital admission for asthma compared with nonvaccinated subjects.[106] Experimentally, it was demonstrated that killed or live *S pneumoniae* administered before, during, or after OVA sensitization attenuated allergic inflammation.[107,108]

The protective role of infection after OVA sensitization increased T_H1 immune response in BALB/c mice, whereas *S pneumoniae* infection during OVA sensitization induced Treg cells and increased IL-10 production.[108] In addition, intranasal administration of pneumococcal conjugate vaccine, but not the polysaccharide vaccine, suppressed allergic immune response and increased Treg cells in the draining lymph nodes, lungs, and spleen.[109] Later, these authors identified pneumococcal components, 3 polysaccharides and pneumolysoid, as key immunoregulators of *S pneumoniae*–induced Treg cells. These components of *S pneumoniae* drove the differentiation of highly suppressive Treg cells, which inhibited T_H2 immune response, prevented the induction of T_H17 immune response, and disabled DC response, resulting in the effective suppression of OVA-induced inflammation,[110] supporting the hygiene hypothesis.[58] Experimental *S pneumoniae* infection in neonatal mice 21 days before OVA sensitization enhanced AHR and increased neutrophil recruitment and T_H17 cells into the airways, whereas IL-17 depletion alleviated airway inflammation mediated mostly by neutrophils, and decreased AHR.[111]

CONCLUSIONS

The interplay between asthma and bacterial infections is complex and involves both asthma and pathogen-specific immune responses. The comorbidities might affect the lung milieu and increase a preexisting T_H2 profile in subjects with allergic asthma (eosinophil inflammation) or drive the immune response to T_H17 profile and generate severe asthma (neutrophil inflammation or granulocytic inflammation). Specific pathogens might activate T_H17 cells that mediate neutrophil influx to the airways, which in turn exacerbates asthma (Fig 3).

It is likely that exacerbation of airway inflammation might require host-directed therapy, depending on the phenotype of asthma and on the comorbidity. The investigation of mediators and receptors using experimental models might provide new molecular targets. The confirmation of these targets is important to delineate immunotherapies or adjuvant therapies based on the concept of host-directed therapies for neutrophilic asthma endotype.

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