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Risks for Infection in Patients With Asthma (or Other Atopic Conditions): Is Asthma More Than a Chronic Airway Disease?

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Abstract

Most of the research effort regarding asthma has been devoted to its causes, therapy, and prognosis. There is also evidence that the presence of asthma can influence patients' susceptibility to infections, yet research in this aspect of asthma has been limited. There is additional debate in this field, with current literature tending to view the increased risk of infection among atopic patients as due to opportunistic infections secondary to airway inflammation, especially in severe atopic diseases. Other evidence, however, suggests that such risk and its underlying immune dysfunction may be a phenotypic or clinical feature of atopic conditions. This review argues that 1) improved understanding of the effects of asthma or other atopic conditions on the risk of microbial infections will bring important and new perspectives to clinical practice, research, and public health concerning atopic conditions and that 2) research efforts into the causes and effects of asthma must be juxtaposed because they are likely to guide each other.

Keywords

adaptive immunity; allergic rhinitis; asthma; atopic dermatitis; epidemiology; immune dysfunction; immune incompetence; infection; innate immunity; phenotype; risk; susceptibility

Introduction

Globally, nearly 300 million people are affected by asthma (4.3-8.6% of adults¹ and 2.8-37% of children² depending on countries). Similarly, significant proportions of people worldwide are affected by atopic dermatitis (1-22%^{2,3} in children and 8-18% in adults³) and allergic rhinitis (2-45% in children² and 7-24% in adults⁵⁻⁸) depending on countries. In the United States, asthma affects a significant proportion of the population (4%-17% of children and 7%-13% of adults) and represents 1 of the 5 most burdensome chronic diseases.⁹⁻¹³ In addition, the prevalence of atopic dermatitis is 10% to 19%,¹⁴⁻¹⁶ affecting 17.8 to 31.6 million people,¹⁴ and the prevalence of allergic rhinitis ranges from 26% to 33%, affecting

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approximately 60 million Americans.¹⁴⁻¹⁷ At present, there are no signs of declining trends in the prevalence of asthma and other atopic conditions; rather, they continue to increase in many parts of the world.^{2,18} Clearly, a significant proportion of people worldwide have been affected by asthma and other atopic conditions. Research in the field of asthma and other atopic conditions has primarily addressed its causes, therapy, and prognosis. For example, research on the role of microbes in the etiology of asthma (whether the role is protective or provocative) has been widely studied, whereas little is known about the burdens to society due to morbidity and mortality resulting from the increased susceptibility to microbial infections that is associated with atopic conditions.

This review aimed to synthesize the current literature on the effects of asthma or other atopic conditions on the risk of microbial infections. Given the paucity of other recent review papers,¹⁹⁻²¹ this review will focus on the emerging literature, expanding our current understanding of the impact of atopic conditions on a broad range of microbial infections from the perspectives of clinical practice, research, and public health.

Effect of Atopic Conditions on the Risk of Microbial Infections

Atopic conditions can increase the risk of infection with several types of organisms in different infection sites. There are several potential causal relationships between atopic conditions and microbial infections or colonization: protective (eg, the “hygiene hypothesis”),^{22,23} provocative (eg, rhinovirus or bacterial colonization),^{24,25} and contextual effects (eg, the microbiome hypothesis),^{26,27} as well as reverse causality^{20,28-30} (Figure 1). This paper focuses on the effect of atopic conditions on the risk of infections, termed *reverse causality*.

Atopic Conditions and Risk of Respiratory Tract Infections

Gram-Positive Bacteria—Previous studies showed significantly increased risks of invasive pneumococcal disease (IPD) and pneumococcal pneumonia in patients with asthma compared with those without asthma (11-17% of the population-attributable risk percent for asthma in invasive pneumococcal diseases).^{28,31-33} A recent systematic review on the association between asthma and risk of IPD also concluded that the risk of IPD was increased among those with asthma.³⁴ The US Advisory Committee on Immunization Practices (ACIP) issued a recommendation in 2008 to give a single dose of 23-valent polysaccharide pneumococcal vaccine (PPV23) to patients with asthma aged 19 to 64 years.³⁵

We reported that both adults and children with atopic dermatitis and/or allergic rhinitis had increased risks of serious pneumococcal diseases compared with those without such conditions; this association was independent of asthma status (adjusted odds ratio [OR], 2.13; 95% CI, 1.04-4.35).²⁹ This was true for upper respiratory pneumococcal infections such as otitis media. Children with asthma or other atopic conditions had higher rates of tympanostomy tube placement (a surrogate marker for frequent and persistent ear infections) than those without asthma (risk ratio [RR], [95% CI]: 1.53 [0.93-2.53] or other atopic conditions (RR: 1.70 [1.01-2.86]).³⁰ Other studies corroborated these study findings with adjusted ORs of 1.40 to 2.70.³⁶⁻³⁹

For other gram-positive bacteria, increased risks of upper respiratory tract infections with *Streptococcus pyogenes* have been reported among children with asthma (adjusted RR, 1.40; 95% CI, 1.12-1.74)⁴⁰ and other atopic conditions (adjusted RR, 1.36; 95% CI, 1.07-1.66, independent of asthma status).⁴¹ Previous studies have shown that asthma was associated with increased colonization with *Streptococcus pneumoniae* and *Staphylococcus aureus* in the nasopharynx.^{42,43,44} Asthmatic patients had an increased risk of *S aureus* colonization as measured by nasal swab (both methicillin-sensitive and methicillin-resistant *S aureus*) based on 2001-2002 NHANES participants older than 1 year (OR, 1.2; 95% CI, 1.0-1.4),⁴³ and another study showed a similar association.⁴⁴ Although the relationship between allergic rhinitis and *S aureus* nasal colonization has been inconsistent,^{45,46} the literature has supported increased risks of *S aureus* colonization of the skin among patients with atopic dermatitis.⁴⁷⁻⁴⁹

Gram-Negative Bacteria—A population-based case-control study was conducted during a major pertussis outbreak in 2004-2005 in Olmsted County, Minnesota. The results showed a significantly increased risk of *Bordetella pertussis* infection among children and adults with versus without asthma (adjusted OR, 1.73; 95% CI, 1.12-2.67; $p=.01$).⁵⁰ Controls for this study were selected from matched individuals who had negative polymerase chain reaction (PCR) test results for pertussis within 1 month of the index date for their corresponding cases. Thus, detection bias (ie, exposure status differentially affecting detection of outcome events) is unlikely to account for the association. Also, neither corticosteroid therapy nor asthma control status was associated with risk of pertussis. The anti-pertussis toxin antibody level was slightly lower in persons with vs without asthma, which may suggest a decreased humoral immune response to *B pertussis* or a more rapid waning of anti-pertussis toxin antibody over time in asthmatic patients. The study concluded that given the high prevalence of asthma and the ongoing risk of pertussis throughout the United States, consideration should be given to defining patients with asthma as a target group for pertussis vaccination (eg, replacing the decennial tetanus-diphtheria booster with tetanus-diphtheria-pertussis vaccine).

Another case-control study showed that asthmatic children had a significantly higher proportion of seropositivity to *Legionella pneumophila* than did nonasthmatic children.⁵¹ Recently, a population-based epidemiologic study showed a significantly increased risk of community-acquired *Escherichia coli* bloodstream infection (BSI) in persons with asthma compared with those without asthma (discussed in the next section).⁵²

Although the mechanisms involved in increased risks of gram-negative bacterial infection among asthma patients is not fully understood, a T-helper 2 cell (Th2)–predominant immune environment in the airways of these patients may have a role. For example, in an *ex vivo* study,⁵³ human bronchial epithelial cells, which were preincubated with interleukin (IL)-4 and IL-13 (Th2 cytokine) for 24 hours and infected with *Pseudomonas aeruginosa*, showed significantly decreased antimicrobial activity. Mice with allergic airway inflammation had significantly more viable bacteria in their lungs and human bronchial epithelial cells had impaired production of antimicrobial peptides such as human β -defensin 2.⁵³ Along these lines, blocking T-helper 1 cell (Th1) cytokines such as IL-12 caused significantly decreased survival rates of affected mice *in vivo*, and administration of exogenous murine recombinant

IL-12 substantially increased survival of mice challenged orally with *Salmonella enterica* Dublin.⁵⁴

Viral Infections—One recent study regarding asthma and viral infections showed that, although asthma status was not associated with the risk of rhinovirus or other viral infections, children with asthma had a significantly higher risk of infection with 2009 novel H1N1 influenza than nonasthmatic children (OR, 4; 95% CI, 1.8-9.0).⁵⁵ Other studies reported both an increased risk of H1N1 infection among children with other atopic conditions (adjusted OR, 1.89; 95% CI, 1.15-3.12)⁵⁶ and more severe H1N1 infection (risk of hospitalization) among those with than without asthma (matched OR, 2.31; 95% CI, 1.13-4.73).⁵⁷ Two independent studies identified asthma as the single most common comorbid condition among patients with severe H1N1 infection (hospitalization or death), with rates of asthma ranging from 10% to 32%.⁵⁸⁻⁶¹

For other viruses, transgenic mice overexpressing IL-4 had significantly delayed clearance of respiratory syncytial virus from the lung compared with control mice.⁶² In another study, more of the subjects with asthma (n=20) had persistently detectable virus 2 weeks after rhinovirus inoculation than did healthy controls (n=17) (60% vs 31%; $p=.06$).⁶³ The potential negative effects of Th2-biased immune conditions on immunity has been further demonstrated for other viruses such as influenza virus,^{64,65} poliovirus,⁶⁶ and human immunodeficiency virus (HIV) infection.⁶⁷⁻⁶⁹ In general, atopic conditions are associated with an increased risk of viral infections, but the risks are affected by the type of virus, the host's immunogenetics, and environmental factors.^{24,70}

Other Microbial Infections—One study showed that patients with asthma were more likely to have *Mycoplasma pneumoniae*-specific IgM antibodies than were those without asthma (39% vs 0%), which may suggest a higher risk of mycoplasma pneumonia in children with stable asthma without recent asthma exacerbation.⁷¹ In another cross-sectional study, asymptomatic asthmatic patients had higher acquisition rates, as measured by reverse transcriptase-PCR, of *M pneumoniae* (45%) and *Chlamydia pneumoniae* (13%), than nonasthmatic persons (9% and 0%, respectively).⁷² The potential negative impact of Th2-biased response on immunity has been further demonstrated for leishmaniasis,⁷³ toxoplasmosis,⁷⁴ schistosomiasis,⁷⁵ and candidiasis.⁷⁶ If patients with asthma and other atopic conditions have normal IgM responses to exposure to microbial organisms (eg, as evidence for mycoplasma infection⁷¹) but suboptimal IgG response as discussed in the mechanism section, these data may suggest some impairment in the immune pathways post-IgM production by B-cells (e.g., impairment in isoclass switching, postswitch defect, or a more rapid waning of humoral immunity).

Taken together, asthma is associated with increased risks of a broad range of common and serious viral and bacterial respiratory infections controlled by different types of immunity. Also, given the association of atopic dermatitis and allergic rhinitis with risks of such infections, the results may imply that immunologic dysfunctions might have a role, while the structural alterations of airways observed in asthma may also need to be taken into account.^{24,77}

Atopic Conditions and Risk of Non-Respiratory Tract Infections

Aside from studies of cutaneous infections (which will not be discussed in this paper),^{19,49} the literature on the relationship between atopic conditions and the risk of non-respiratory tract infections is limited. This section summarizes the currently available literature on the effects of asthma or other atopic conditions on risk of infection other than the airways.

Genitourinary Tract Infection—Community-acquired *E coli* BSI is the most common cause of BSI in adults and young infants, and the primary source of infection is the urinary and gastrointestinal tract.⁷⁸ We recently reported the association between asthma and an increased risk of community-acquired *E coli* BSI in a population-based case-control study (adjusted OR, 2.74; 95% CI, 1.11-6.76; $P=.03$).⁵² Food allergy only approached statistical significance for the association (adjusted OR, 3.51; 95% CI, 0.94-13.1; $p=.06$), and other atopic conditions were not associated. In our study, there was no evidence of a differential asthma effect across age strata. In support of this finding, Jackson et al⁷⁹ reported a higher risk of community-acquired *E coli* BSI among adults older than 65 years with asthma (5.5%, vs 1%). Koch et al⁸⁰ reported impaired Th1-immune response (IL-12-induced interferon [IFN]- γ release from T cells) to endotoxin from *Salmonella enteritidis* in patients with asthma. Also, a recent mouse study showed that IL-13-deficient mice (lack of Th2-type immune response associated with atopic conditions) showed a significantly lower rate of intravaginal infection after intravaginal inoculation with *Chlamydia* than did wild-type mice.⁸¹ This result suggests a Th2-type immune response associated with atopic conditions increases susceptibility to genital tract infection.

Reactivation of Latent Viral Infection—In addressing the relationship between asthma and risk of microbial infections, herpes zoster provides an important insight into the effects of asthma on susceptibility to infections, for several reasons. First, infection is due to reactivation of varicella zoster virus from a latent state in dorsal root ganglia rather than primary respiratory tract or skin infection. Second, the main defense mechanism is cell-mediated immunity (CMI) instead of innate or humoral immunity. And third, it is a vaccine-preventable disease unlike herpes simplex infection.⁸²⁻⁹⁰ We recently conducted a population-based study showing that asthma led to a significantly increased risk of herpes zoster in children (adjusted OR, 2.09; 95% CI, 1.24-3.52).⁹¹ The population-attributable risk percent of herpes zoster for patients with asthma was estimated to be 12%. The presence of sensitization against aeroallergen or food allergen was also associated with an increased risk of herpes zoster (matched OR, 3.00; 95% CI, 1.09-8.25) on univariate analysis. A National Institutes of Health-funded study is currently investigating whether the same is true for adults with asthma. A large retrospective cohort study showed that asthma (>3 acute exacerbations before the index date) was the most common chronic condition among children with herpes zoster.⁹² Previous studies showed that persons with atopic conditions (asthma, atopic dermatitis, or allergic rhinitis) have increased risks of herpes simplex ocular infections.^{93,94}

Although the results need to be replicated in adults, our study findings suggest that the effects of asthma on risk of infection may not be limited to the airways but go beyond

airways. Furthermore, CMI against herpes zoster or other herpes viruses may be compromised in patients with asthma.

Potential Factors Affecting the Association Between Atopic Conditions and Risk of Microbial Infection

Although many potential factors can be related to the association between atopic conditions and risk of microbial infection, we focus this discussion on corticosteroid therapies and control status of asthma.

Influence of Corticosteroid Therapies on Risk of Infections

Use of inhaled corticosteroid (ICS) has been reported to increase the risk of infections (eg, pneumonia) in patients with chronic obstructive pulmonary disease, but this finding has not been established in patients with asthma.⁹⁵⁻⁹⁸ O'Byrne et al reported that ICS therapy was not associated with risk of pneumonia as a serious adverse event among asthmatic patients (hazard ratio, 1.29; 95% CI, 0.53-3.12). Interestingly, ICS even decreased the risk of pneumonia as an adverse event in patients with asthma (hazard ratio, 0.52; 95% CI, 0.36-0.76), on the basis of pooled data from many clinical trials.⁹⁷ The association was not affected by the dose, type, or duration of ICS. Also, oral corticosteroid therapy among patients using vitamin D was not associated with increased risk of pneumonia but decreased the risk of pneumonia.⁹⁹ The study findings described above on the association of asthma with the increased risks of serious pneumococcal disease,²⁸ *B pertussis*,⁵⁰ *S pyogenes* upper respiratory infections,⁴⁰ recurrent/persistent otitis media,³⁰ H1N1 influenza,⁵⁶ community-acquired *E coli* BSI,⁵² and herpes zoster⁹¹ among patients with asthma were independent of the use of inhaled or systemic corticosteroids. Talbot et al³¹ reported similar findings. Furthermore, systemic corticosteroid therapy was not associated with decreased humoral or cell-mediated responses to vaccines.^{96,100-103}

A study comparing ICS treatment versus placebo showed a significant decrease from before to after therapy in the percentage of days of upper respiratory tract infection (21% to 10% ICS vs 19% to 16% placebo) and lower respiratory tract infection (30% to 15% ICS vs 27% to 21% placebo).¹⁰⁴ Another study in patients with asthma gave an estimated OR of 0.34 for the association between treatment with corticosteroids and the risk of mycoplasma or chlamydia infections ($p=.07$), which suggests that corticosteroid treatment may have a protective effect for the risk of these infections.⁷² Taken together, corticosteroid therapies are unlikely to account for the association of asthma and other atopic conditions with the increased risks of microbial infections.

Asthma Control Status or Severity and Risk of Infections

Intuitively, the increased risk of infections among persons with severe or poorly controlled asthma may not be surprising given the potential negative effects of inflammation on the airway architecture.^{31,33} The question of whether those with mild asthma are at an increased risk of infection, however, is important given the relatively larger proportion of patients with mild or inactive asthma than moderate/severe asthma at a population level (60% vs 40% in the United States¹⁰⁵ and 63%-65% vs 35%-37% in Europe).¹⁰⁵⁻¹⁰⁷ Although Talbot et al³¹

reported an increased risk of IPD among patients with low-risk asthma (OR, 1.77; 95% CI, 0.99-3.0), high-risk asthma was responsible for 83% of IPD cases in Medicaid patients in Tennessee. In contrast, Klemets et al³³ found that only 13% of high-risk asthma accounted for IPD in a Finnish national database. Underrepresentation of low-risk asthma in the study by Talbot et al³¹ is not surprising since the Medicaid population used in that study disproportionately represents a population with more severe asthma, increased health care utilization for asthma, and higher mortality for asthma.¹⁰⁸

Klemets et al³³ suggested that low-risk asthma (no hospitalization during the 12 months before the index date) significantly increased the risk of IPD (OR, 2.8; 95% CI, 2.1-3.6) and accounted for 87% of IPD cases. Since the definition of low-risk asthma is relatively broad, it is difficult to determine the extent to which asthma control status contributes to the risk of infections. However, patients with high-risk asthma accounted for a smaller proportion of those with IPD than did patients with low-risk asthma. This finding may be consistent with our previous study results showing no significant differences between children who did and did not achieve remission of asthma in the incidence of viral infections (0.3; 95% CI, 0.2-0.8 vs 0.4; 95% CI, 0.1-0.7, respectively) or bacterial infections (0.5; 95% CI, 0.2-1.0 vs 0.5; 95% CI, 0.2-0.9, respectively) in the first 18 years after the onset of asthma.¹⁰⁹ Also, the associations of asthma with the increased risks of pertussis,⁵⁰ *S pyogenes* upper respiratory infection,⁴⁰ and herpes zoster⁹¹ were independent of asthma control status or severity. Therefore, the current literature suggests that the asthma-associated risks of infections are unlikely to be limited to only those with severe or poorly controlled asthma but include those with mild or well-controlled asthma.

In this respect, the current ACIP recommendation for PPV23 for patients with asthma includes all patients, regardless of the current asthma control status or severity. This approach appears to make sense on the basis of the current scientific evidence. Along these lines, although the causal inference can be bidirectional, there is some evidence that the effect of atopic conditions on the risk of microbial infections or immune dysfunction might begin before the onset of clinical asthma.^{25,30,40} These findings may be consistent with the notion that some phenotypic features of asthma (eg, poor lung function) begin before the development of clinical asthma in children (ie, the “hypothesis of early programming of asthma”).¹¹⁰⁻¹¹⁴

Potential Mechanisms Underlying the Association Between Atopic Conditions and Increased Risk of Microbial Infections

The immunological abnormalities and dysfunctions associated with atopic conditions reported in the literature are summarized in Table E1 (see the online repository). As this is an active research area, the information in Table E1 will need to be frequently updated as new results are emerging. However, the summary provides potential biological mechanisms for the epidemiological association between atopic conditions and the increased risk of microbial infections.

Innate Immunity

Innate immune dysfunction and Th2-immune response at the level of epithelial cells and the immune system in patients with asthma have been well established.¹¹⁵⁻¹²² The discovered mechanisms are pertinent to the increased risk of viral infections (eg, impaired secretion of IFN- β and - λ by bronchial epithelial cells)^{117,118} and bacterial infections (eg, impaired Toll-like receptor 2-mediated signal transduction recruiting neutrophils)^{53,115} in patients with atopic conditions. However, impairment of innate immunity appears to occur only in a subgroup of patients with asthma.¹²³ Although impaired innate immunity accounts for the association between atopic conditions and increased risks of certain microbial infections, it might not be sufficient to explain the increased risk of all infections, such as vaccine-preventable infections or invasive disease, as summarized in Figure E1 (see the online repository).

Humoral Immunity

Some impairment in adaptive immunity in patients with atopic conditions is likely to contribute to increased susceptibility to serious and common microbial infections, especially vaccine-preventable infectious diseases. An early study comparing humoral immunity between asthmatic patients (who were not taking corticosteroids) and normal controls found that 13 of 74 asthmatic patients (18%) and 1 of 74 controls (1.3%) had no response to tetanus toxoid ($p < .001$).¹²⁴ This observation was also true for atopic dermatitis (10% vs 0%, $p < .04$).¹²⁵ A subsequent study comparing antibody levels before and after PPV23 vaccination in children aged 2 to 18 years found that those with asthma had much lower antibody levels against the studied polysaccharide antigens than children without asthma both before and after vaccination.¹⁰¹ In another study in children aged 3 to 8 years, 17% of children with eczema responded to PPV23 compared with 57% of children without eczema (OR, 0.2; 95% CI, 0.05-0.84; $p = .03$).¹²⁶ This also was true for antibody responses to other vaccines. We also found Somali immigrants with asthma who spent their early childhood in Africa had a poorer IgG response to mumps vaccine virus than did those without asthma.¹²⁷

We recently found significantly lower serotype-specific pneumococcal antibody titers in asthmatic patients than nonasthmatic persons (8.5 and 15.5 of 23 serotypes, respectively, $p = .03$) and an inverse relationship between the ratio of IL-5 to IFN- γ secretion by peripheral blood mononuclear cells after stimulation with house dust mites and the number of positive serotype-specific antibodies ($r = -0.36$, $p = .052$).¹¹⁶ Lower serotype-specific pneumococcal antibody responses (IgG) were related to alleles associated with atopy and asthma (IL-4 -589T, IL-4 2979T and IL-4R alpha 551Gln) among children with recurrent otitis media aged 1-7 years who participated in a pneumococcal vaccine trial.¹²⁸ Although there was no difference in pneumococcal surface protein antibody levels between patients with and without asthma, Th2-immune response to staphylococcal enterotoxin B was also inversely correlated with anti-pneumococcal surface protein C (PspC) antibody levels ($r = -0.53$, $p = .003$). This correlation was significantly modified by asthma status: $r = -0.74$, $p = .001$ for asthmatic patients vs $r = -0.06$, $p = .83$ for nonasthmatic persons.¹²⁹ Also, serum 25-hydroxyvitamin D levels were associated with pneumococcal antibody levels, and the association was modified by asthma and other atopic conditions.^{130,131} Children with asthma or house dust mite sensitization had significantly lower IgG₁ titers against

Haemophilus influenza antigens (P4 and P6) and PspC than children without asthma or those without house dust mite sensitization at age 5 years.¹³² Children with house dust mite sensitization had lower PspA titers at age 3 years. Asthmatic patients had slightly lower anti-pertussis toxin antibody levels than those without asthma.⁵⁰ Th2-cytokines (IL-4) negatively affected antibody responses to pneumococcal polysaccharide antigens, whereas Th1 cytokines (IFN- γ) positively affected the antibody responses in an *in vivo* mouse study that assessed humoral immune response to intact *S pneumoniae*.^{133,134} Our recent study showed that children with asthma, who had received one dose of MMR vaccine, had a more rapid waning of measles vaccine virus-specific IgG levels over time (a decrease of -0.114 unit per year vs. -0.046 unit per year, $p=0.01$) resulting in a lower seropositive rate than those without asthma (73 vs. 84%, $p=0.038$). Similarly, children who developed asthma subsequently had a more rapid waning of anti-measles antibody levels than non-asthmatics.¹³⁵ Indeed, a previous cross-sectional study reported that a substantial percentage of children (age 1.6-17 years) with asthma who had received 2 doses of MMR were found to be seronegative for measles (40%-43%) and mumps (25%-39%).¹³⁶

In contrast to these potential intrinsic adaptive immune dysfunctions, we recently reported the association between asthma and selective IgA deficiency (sIgAD)/common variable immunodeficiency (CVID).¹³⁷ A history of asthma before the index date of sIgAD/CVID (OR, 2.77; 95% CI, 1.09-7.06) and a history of asthma (before or after the index date of sIgAD/CVID) was more prevalent in sIgAD/CVID cases than in their matched controls (OR, 3.57; 95% CI, 1.50-8.51). These data suggest that asthma or its underlying immune mechanisms might affect kinetics in the maturation of B cells into IgA- (or other immunoglobulin)-producing plasma cells (eg, isotype switching defect or postswitch defect).¹³⁸⁻¹⁴⁰ Mutations in the *TNFRSF13B* gene (TACI gene-transmembrane activator and calcium-modulator and cyclophilin ligand interactor) are found in 6.25% of sIgAD and 8% to 21% of CVID patients.^{141,142} A recent study showed that Swedish children with *TNFRSF13B* mutations had a 2.5-fold increased risk of asthma at 4 years, independent of IgE levels.¹⁴³ Although further studies are needed to determine the exact mechanisms underlying this association, the study findings highlight potential humoral immune dysfunctions in patients with asthma.

Cell-Mediated Immunity

An early study reported that 9.2% (8/87) of asthmatic children and adults and 1.2% (1/86) of persons without asthma had no delayed-type hypersensitivity (CMI) response to any of fungal, viral, and tuberculous antigens ($p<.02$) (see Table E1).¹²⁴ This was also true for those with and without atopic dermatitis (45% vs 27%; $p<.001$).¹²⁵ Shirakawa et al reported an inverse correlation between IgE levels and risk of atopic conditions, and the degree of tuberculin response as a marker for CMI, which might suggest a potential negative influence of atopy and atopic conditions on CMI.¹⁴⁴ Innate and humoral immune dysfunctions alone are unlikely to fully explain the study findings on the increased risk of herpes zoster in patients with asthma⁹¹ because most children and almost all adults aged 40 years or older in the United States (>99%) have evidence of serologic immunity to varicella zoster and stable humoral immunity over time.^{82,145} In addition, CMI has been known to be the primary defense mechanism against herpes zoster.^{82,84,146} Persons with atopic dermatitis

complicated with herpes simplex virus infection had significantly fewer IFN- γ spot-forming cells and less IFN- γ secretion by peripheral blood mononuclear cells after stimulation with herpes simplex virus than did controls, which suggests that impaired CMI alone can result in increased risk of severe eczema herpeticum.¹⁴⁷

Little is known about the influence of asthma and other atopic conditions on vaccine-induced immune response. Two recent studies also showed impaired CMI after nonspecific stimulation in patients with asthma or atopic dermatitis, but antigen-specific CMI was not impaired.^{148,149} We recently assessed CMI responses to the viruses in the measles, mumps, and rubella (MMR) vaccine among children aged 12 to 18 years who had received 2 doses of the MMR vaccine. Asthmatic patients with a family history of asthma had significantly poorer CMI responses to MMR vaccine viruses than did those without asthma.¹⁵⁰ As observed in humoral immunity against measles vaccine virus, this suboptimal CMI in children with asthma might be explained by decreased immune response to vaccine and/or rapid waning of immunity over time, given the reported waning of immunity against measles (–1.6% per year)^{151–153} and rubella (–2.9% per year).¹⁵³

Summary of the mechanisms

Impaired innate immunity against bacteria (eg, pneumococci) may increase the risk of bacterial colonization and infection in the airways of asthmatic patients.¹¹⁵ However, this impairment in innate immunity alone may not be sufficient to cause certain infections such as vaccine-preventable infection or invasive bacterial infection in atopic patients. For example, opsonization of pneumococci by capsular antigen-specific antibody is a crucial mechanism for clearing pneumococci from the bloodstream by the spleen and prevents invasive diseases caused by capsular organisms.^{154,155} The conceptual proposition for the association between asthma and risk of infection is summarized in Figure E1. It highlights that immune dysfunction in atopic patients might contribute to each stage of microbial infection from colonization to severe invasive microbial infection in the context of genetic and environmental factors. A question remains, however, why some atopic patients have development of or recover from each stage of infection and others do not. Immunogenetic mechanisms underlying atopic conditions in conjunction with environmental factors may be related to T-cell or B-cell maturational development and kinetics in a way affecting adaptive immune competence and, in turn, susceptibility to certain microbial infections.

Implications

Patient Care

First, while clinicians and patients with asthma need to make a concerted effort to control asthma to reduce risks of microbial infections, patients with asthma aged 19 to 64 years should be vaccinated with PPV23 regardless of their asthma control status. The current ACIP recommendation does not limit PPV23 vaccinations to only patients with severe or poorly controlled asthma because of the increased risk of IPD among those with mild asthma. For young adults with asthma that is well controlled or in remission, clinicians should at least discuss the benefits and risks of PPV23 vaccinations. This is particularly true for young adults with asthma who smoke cigarettes, which is another indication for PPV23.

This unique population should be a potential target group for PPV23 vaccination, counseling, and asthma management planning.

Second, given the significant proportion of children and adults affected by atopic conditions and their increased risk of infections, clinicians might consider more careful evaluation of those with serious infection (eg, BSI) or frequent common infections (eg, otitis media or *S pyogenes* infection) to discern whether a patient has undetected clinical asthma or other atopic conditions, instead of solely seeking primary immunodeficiency. If an atopic condition is found, a specific immune deficiency work-up including measurement of immunoglobulin levels (IgG, IgA, and IgM) can be considered given the association of asthma with sIgAD and CVID, which are the 2 most common primary immunodeficiencies. If an initial work-up for immune deficiency is normal, it may be permissible for clinicians not to routinely pursue extensive immune deficiency work-up for otherwise healthy asthmatic patients with frequent common infections (eg, ear infection) until more specific immune function tests are available for atopic patients with increased risk of infections and immune incompetence. Nonetheless, the information discussed in this paper might be useful for clinicians in counseling otherwise healthy asthmatic or atopic patients with normal immune functions who are frustrated by their frequent microbial infections and lack of clear answer.

The role of antibiotic therapy or prophylaxis for atopic patients with frequent bacterial infections must be studied in terms of its risks and benefits. If a patient with an atopic condition has a vaccine-preventable infection such as pertussis, it would be prudent to check the person's humoral immunity to its associated vaccines (eg, diphtheria and tetanus). If humoral immunity has waned and the patient is seronegative, a booster should be given and vaccine response should be checked. This type of patient might be at high risk for waning of vaccine-induced immunity over time and should be carefully followed up.

Third, given the significantly increased risk of microbial infections, it is important for both clinicians and patients with asthma and other atopic conditions to meet the guidelines for all routine vaccinations. For example, given recent outbreaks of pertussis,¹⁵⁶ the substantial risk of pertussis among asthmatic patients, and the considerable number of Americans with asthma, adolescents and adults should receive a single dose of tetanus-diphtheria-pertussis vaccine according to the recommended schedule. In addition, given the low influenza vaccine uptake rate (40%)^{157,158} and higher risk and severity of influenza in individuals with asthma and other atopic conditions, clinicians and related agencies should develop strategies to improve the influenza vaccine uptake rate.

Research

First, in characterizing asthma in terms of phenotypes or endotypes, it might be time to consider incorporating both susceptibility to microbial infections and measurable immune incompetence into the currently recommended predictor and outcome variables for asthma research. Currently, neither the PRACTALL (PRACtical ALLergy) consensus report suggesting a framework for asthma phenotypes/endotypes,¹⁵⁹ nor the National Heart, Lung, and Blood Institute-sponsored workshop report standardizing predictor and outcome variables for asthma research,¹⁶⁰ recommended including risks of serious or common

infections or immunological parameters concerning immune incompetence against microbial organisms as measures for asthma research. Likewise, none of the previous studies that attempted to identify phenotypic clusters of asthmatic patients incorporated susceptibility to infection or immune dysfunction in the analysis but only focused on atopic features and airway functions.¹⁶¹⁻¹⁶⁷ This may result in a significant underestimation of the impact of asthma on morbidity and mortality and may deter proper understanding of the heterogeneity of asthma. Thus, research on the effects of asthma must parallel research on etiologic, therapeutic, and prognostic factors because they guide each other.

Second, it is likely that only a subgroup of patients with asthma and other atopic conditions have increased risks of microbial infections and immune incompetence. However, it is unknown what proportion of patients with asthma or other atopic conditions are more susceptible to serious or common microbial infections than others and what characterizes these individuals. For example, given the incidence of *S pyogenes* infection among healthy children without asthma or other atopic conditions (18 per 100 person-years), the numbers needed to treat for a common infection like *S pyogenes* upper respiratory infection due to asthma and other atopic conditions were estimated to be 14 ($\approx 7\%$ incidence rate difference) and 16 ($\approx 6\%$ incidence rate difference), respectively.^{40,41} Although, individually, asthma and other atopic conditions only approach a 10% incidence rate difference (a presumptive minimally important change, or a 1-digit change in number needed to treat, would be greater than a 10% incidence rate difference), collectively, they might exceed 10%. Thus, it would be important to develop a strategy to identify a subgroup of patients with asthma or other atopic conditions who have increased risk of microbial infections or underlying immune incompetence. To accomplish this goal, both epidemiological research, which better characterizes patients with atopic conditions, and laboratory research, which develops suitable immunological assays measuring immune incompetence associated with atopic conditions, are needed, since traditional immune work-ups are unlikely to reveal such immune dysfunction associated with atopic conditions.

Finally, the effects of atopic conditions or effects of local inflammatory responses may not be limited to the airways but rather may be systemic. This concept is theoretically possible, since some of the important immune cells (eg, T cells or dendritic cells) originate from bone marrow and are recruited to the organs by specific signals and because bone marrow and airways interact.^{24,168} Thus, it will be necessary to consider the broader clinical and immunological features of atopic conditions other than airway features, which might suit the emerging literature on a broader range of T cells and their functions, including their immunologic plasticity.¹⁶⁹ Such efforts will also help us narrow down or better characterize asthma phenotypes. One could speculate that asthma includes clinical and laboratory features of both inflammation and immune incompetence at systemic and airway levels, through abnormal functions and kinetics of effector and/or memory immune cells involving in innate and adaptive immunity, at least in a subgroup of asthmatic patients. Alternatively, this subgroup of patients may not have asthma but an immune disorder unrecognized or undefined, which should be labeled otherwise. Although this understanding might challenge the traditional understanding of asthma as an airway disease, it will provide a basis for a broader conceptual understanding of asthma, which allows for reinterpretation of

inconsistent epidemiologic and laboratory study results (eg, genomewide association studies) and a more suitable classification of asthma phenotypes and endotypes in the future.

Public Health

Knowledge of the potential effects of atopic conditions on the risk of various microbial infections will provide an important basis for public health surveillance of these effects and the epidemiology of a broad range of microbial infections. The effects of atopic conditions on emerging or re-emerging infectious diseases at a population level are unknown. The proportion of persons with atopic conditions in a given population that is affected by emerging or re-emerging infectious diseases may have important effects on public health. This emerging research trend calls for systematic study of the effect of asthma or other atopic conditions on a broad range of health outcomes in the future.

Conclusions

Atopic disease ranging from mild to severe increases a person's susceptibility to various respiratory and nonrespiratory microbial infections with different degrees of impact. The impact of asthma on the risk of microbial infection resulted in a change of vaccination schedule in the United States. Impairment in both innate and adaptive immunity underlies the association. It is necessary to consider the increased susceptibility to serious and common infections and the underlying immune dysfunctions as a potential feature of atopic conditions, instead of regarding the infections as opportunistic or as events secondary to airway inflammation. These clinical and laboratory features of atopic conditions might be suitably coupled with the conceptual understanding of atopic conditions as both systemic and airway diseases. As the previously unrecognized effects of atopic conditions on the risks of various infectious diseases emerge, patient care for atopic conditions will be increasingly necessary to address areas not being addressed by the current guidelines. Also, the roles of allergists, immunologists, and pulmonologists may be broader in the future. Therefore, the current guidelines for asthma or other atopic conditions may, in the future, need to address a broader range of management issues for infectious diseases among these patients. This review paper provides an insight into these foreseeable needs and challenges.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACIP	Advisory Committee on Immunization Practices
BSI	bloodstream infection
CMI	cell-mediated immunity
CVID	common variable immunodeficiency
HIV	human immunodeficiency virus
ICS	inhaled corticosteroid
IFN	interferon
IL	interleukin
IPD	invasive pneumococcal disease
MMR	measles, mumps, and rubella
OR	odds ratio
PCR	polymerase chain reaction
PPV23	23-valent pneumococcal polysaccharide vaccine
PspC	pneumococcal surface protein C
RR	risk ratio
sIgAD	selective IgA deficiency
Th1	T-helper 1 cell
Th2	T-helper 2 cell

Summary

What do we know?

1. Patients with asthma and other atopic conditions have significantly increased risks of serious and common infections with both viruses and bacteria.
2. Atopic disease ranging from mild to severe increases a person's susceptibility to both respiratory and nonrespiratory microbial infections.
3. A subgroup of patients with asthma and other atopic conditions have impairments in innate immunity in the airways and decreased adaptive immune functions.

What is still unknown?

1. The molecular mechanisms for how atopic conditions impair immune functions to make patients susceptible to microbial infections are unclear, as is the extent to which such impairment contributes to the risk of microbial infections among these individuals.
2. Clinical features and biomarkers must be determined for identifying patients with asthma or other atopic conditions who have increased susceptibility to infections and immune incompetence and distinguishing them from those without such features.
3. The extent to which atopic conditions affect the epidemiology of emerging and re-emerging infectious diseases at a population level is not known.

Figure 1.

The relationship between microbial colonization or infections and atopic conditions. This diagram suggests a bidirectional causal relationship between exposure to microbial colonization or infection and risk of atopic conditions, which encompasses four specific hypotheses: the 'hygiene hypothesis', the 'counter-hygiene hypothesis', the 'microbiome hypothesis', and reverse causality. The 'hygiene hypothesis' suggests exposure to microbial colonization or infection during early childhood provides a protective effect on the development of atopic conditions whereas the 'counter-hygiene hypothesis' suggests a provocative effect of exposure to microbial infection during early childhood on the development of atopic conditions (eg, human rhinovirus infection). The recent microbiome hypothesis suggests a contextual effect of such exposure on the development of atopic conditions depending on diversity of microbiome. While these hypotheses address a causal direction for the influence of exposure to microbial organisms on the development of atopic conditions, reverse causality hypothesis argues for a causal direction that atopic conditions alter susceptibility to microbial colonization or infections.