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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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1. To provide examples of specific immune dysfunction that might contribute to increased risk of infection in patients with asthma.
2. To recognize asthma of all severities as a risk factor for respiratory and nonrespiratory tract infections.

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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 caused by opportunistic infections secondary to airway inflammation, especially in patients with severe atopic diseases. However, other evidence suggests that such risk and its underlying immune dysfunction might be a phenotypic or clinical feature of atopic conditions. This review argues (1) that 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 (2) that research efforts into the causes and effects of asthma must be juxtaposed because they are likely to guide each other. (J Allergy Clin Immunol 2014;134:247-57.)

Key words: *Adaptive immunity, allergic rhinitis, asthma, atopic dermatitis, epidemiology, immune dysfunction, immune incompetence, infection, innate immunity, phenotype, risk, susceptibility*

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Globally, nearly 300 million persons are affected by asthma (4.3% to 8.6% of adults[1] and 2.8% to 37% of children,[2] depending on the country). Similarly, significant proportions of persons worldwide are affected by atopic dermatitis (1% to 22%[2,3] in children and 8% to 18% in adults[4]) and allergic rhinitis (2% to

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Abbreviations used
ACIP: Advisory Committee on Immunization Practices
BSI: Bloodstream infection
CMI: Cell-mediated immunity
CVID: Common variable immunodeficiency
ICS: Inhaled corticosteroid
IPD: Invasive pneumococcal disease
MMR: Measles, mumps, and rubella
OR: Odds ratio
PPV23: 23-Valent pneumococcal polysaccharide vaccine
RR: Risk ratio
sIgAD: Selective IgA deficiency

45% in children[2] and 7% to 24% in adults[5-8]), depending on the country. In the United States asthma affects a significant proportion of the population (4% to 17% of children and 7% to 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 persons,[14] and the prevalence of allergic rhinitis ranges from 26% to 33%, affecting approximately 60 million Americans.[14-17] At present, there are no signs of decreasing 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 persons worldwide have been affected by asthma and other atopic conditions. Research in the field of asthma and other atopic conditions has primarily addressed causes, therapy, and prognosis. For example, the role of microbes in the cause of asthma (whether the role is protective or provocative) has been widely studied, whereas little is known about the burdens to society caused by morbidity and mortality resulting from the increased susceptibility to microbial infections 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 articles,[19-21] this review will focus on the emerging literature, expanding our current understanding of the effect 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 at 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 (eg, the microbiome hypothesis)[26,27] effects, as well as reverse causality[20,28-30] (Fig 1). This article focuses on the effect of atopic conditions on the risk of infections, which is termed reverse causality.

Atopic conditions and risk of respiratory tract infections

Gram-positive bacteria. Previous studies showed a significantly increased risk of invasive pneumococcal disease (IPD) and pneumococcal pneumonia in patients with asthma

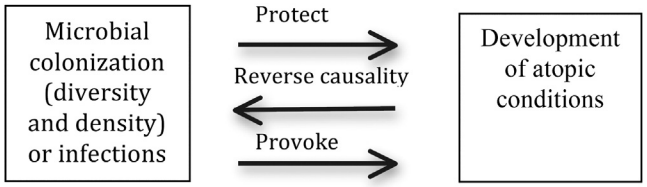

FIG 1. Relationship between microbial colonization or infections and atopic conditions. This diagram suggests a bidirectional causal relationship between exposure to microbial colonization or infection and risk of atopic conditions, which encompasses 4 specific hypotheses: the hygiene hypothesis, the 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 the diversity of the microbiome. Although these hypotheses address a causal direction for the influence of exposure to microbial organisms on the development of atopic conditions, the reverse causality hypothesis argues for a causal direction that atopic conditions alter susceptibility to microbial colonization or infections.

compared with those without asthma (11% to 17% of the population-attributable risk percentage for asthma in patients with IPD).[28,31-33] A recent systematic review on the association between asthma and the risk of IPD also concluded that this risk was increased in asthmatic patients.[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 asthmatic patients aged 19 to 64 years.[35]

We reported that both adults and children with atopic dermatitis, allergic rhinitis, or both had increased risk of serious pneumococcal disease 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 tract 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], 1.53; 95% CI, 0.93-2.53) or other atopic conditions (RR, 1.70; 95% CI, 1.01-2.86).[30] Other studies corroborated these findings with adjusted ORs of 1.40 to 2.70.[36-39]

For other gram-positive bacteria, an increased risk of upper respiratory tract infections with *Streptococcus pyogenes* has 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.[42-44] Asthmatic patients had an increased risk of *S aureus* colonization, as measured by using nasal swabs (both methicillin-sensitive and methicillin-resistant *S aureus*), based on 2001-2002 National Health and Nutrition Examination Survey 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 an increased risk of *S aureus* colonization of the skin in 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 those without asthma (adjusted OR, 1.73; 95% CI, 1.12-2.67; $P = .01$).[50] Control subjects for this study were selected from matched subjects who had negative 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 versus those without asthma, which might 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 risk of gram-negative bacterial infection among asthmatic patients is not fully understood, a T_H2-predominant immune environment in the airways of these patients might have a role. For example, in an *ex vivo* study[53] human bronchial epithelial cells, which were preincubated with IL-4 and IL-13 (T_H2 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_H1 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, asthmatic children 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 asthmatic patients (n = 20) had persistently detectable virus 2 weeks after rhinovirus inoculation than did healthy control subjects (n = 17; 60% vs 31%, $P = .06$).[63] The potential negative effects of T_H2-biased immune conditions on immunity has been further demonstrated for other viruses, such as influenza virus,[64,65] poliovirus,[66] and 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 might suggest a higher risk of *M pneumoniae* infection in children with stable asthma and without a recent asthma exacerbation.[71] In another cross-sectional study asymptomatic asthmatic patients had higher acquisition rates, as measured by using RT-PCR, of *M pneumoniae* (45%) and *Chlamydia pneumoniae* (13%) than nonasthmatic subjects (9% and 0%, respectively).[72] The potential negative effect of a T_H2-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* species infection[71]) but suboptimal IgG response, as discussed in the mechanism section, these data might suggest some impairment in the immune pathways after IgM production by B cells (eg, 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 tract infections controlled by different types of immunity. Also, given the association of atopic dermatitis and allergic rhinitis with risks of such infections, the results might imply that immunologic dysfunctions might have a role, although the structural airway alterations observed in asthmatic patients might 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 article),[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 the risk of infections other than those found in 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 al[79] reported a higher risk of

community-acquired *E coli* BSI among asthmatic adults older than 65 years (5.5% vs 1%). Koch et al[80] reported an impaired T_H1 immune response (IL-12–induced IFN-γ release from T cells) to endotoxin from *Salmonella enteriditis* in asthmatic patients. Also, a recent mouse study showed that IL-13–deficient mice (lack of T_H2-type immune response associated with atopic conditions) had a significantly lower rate of intravaginal infection after intravaginal inoculation with *Chlamydia* species than seen in wild-type mice.[81] This result suggests that a T_H2-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 the 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. 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 percentage of herpes zoster for patients with asthma was estimated to be 12%. The presence of sensitization against aeroallergens or food allergens was also associated with an increased risk of herpes zoster infection (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 asthmatic adults. 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 an increased risk of herpes simplex ocular infection.[93,94]

Although the results need to be replicated in adults, our study findings suggest that the effects of asthma on the risk of infection might not be limited to the airways. Furthermore, CMI against herpes zoster or other herpes viruses might be compromised in asthmatic patients.

POTENTIAL FACTORS AFFECTING THE ASSOCIATION BETWEEN ATOPIC CONDITIONS AND THE RISK OF MICROBIAL INFECTION

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

Influence of corticosteroid therapies on infection risk

Use of inhaled corticosteroids (ICSs) 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 asthmatic patients.[95-98] O'Byrne et al[97] reported that ICS therapy was not associated with the risk of pneumonia as a serious adverse event among asthmatic patients (hazard ratio, 1.29; 95% CI, 0.53-3.12). Interestingly, ICSs even decreased the risk of pneumonia as an adverse event in asthmatic patients (hazard ratio, 0.52; 95% CI, 0.36-0.76) based on pooled data from many clinical trials. The association was not affected by the dose, type, or duration of ICS use. Also, oral corticosteroid therapy among patients using vitamin D was not associated with increased risk of pneumonia but rather decreased this risk.[99] The study findings described above on the association of asthma with an increased risk of serious pneumococcal disease,[28] *B pertussis*,[50] *S pyogenes* upper respiratory tract infections,[40] recurrent/persistent otitis media,[30] H1N1 influenza,[56] community-acquired *E coli* BSI,[52] and herpes zoster[91] among asthmatic patients were independent of the use of ICSs or systemic corticosteroids. Talbot et al[31] 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 (21% to 10% for ICS vs 19% to 16% for placebo) and lower (30% to 15% for ICS vs 27% to 21% for placebo) respiratory tract infection.[104] Another study in asthmatic patients produced an estimated OR of 0.34 for the association between treatment with corticosteroids and the risk of *Mycoplasma* or *Chlamydia* species infections ($P = .07$), which suggests that corticosteroid treatment might have a protective effect on this risk.[72] Taken together, corticosteroid therapies are unlikely to account for the association of asthma and other atopic conditions with the increased risk 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 might not be surprising given the potential negative effects of inflammation on the airway architecture.[31,33] However, the question of whether those with mild asthma are at an increased risk of infection is important given the relatively larger proportion of patients with mild or inactive asthma than moderate-to-severe asthma at a population level (60% vs 40% in the United States[105] and 63% to 65% vs 35% to 37% in Europe).[105-107] Although Talbot et al[31] 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 al[33] found that only 13% of cases of high-risk asthma accounted for IPD in a Finnish national database. Underrepresentation of low-risk asthma in the study by Talbot et al[31] is not surprising because the Medicaid population used in that study disproportionately represents a population with more severe asthma and increased health care use and higher mortality caused by asthma.[108]

Klemets et al[33] 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. Because 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 infection. However, patients with high-risk asthma accounted for a smaller proportion of those with IPD than did patients with low-risk asthma. This finding might be consistent with our previous

study results showing no significant differences between children who did and did not achieve asthma remission in the incidence of viral (0.3 [95% CI, 0.2-0.8] vs 0.4 [95% CI, 0.1-0.7], respectively) or bacterial (0.5 [95% CI, 0.2-1.0] vs 0.5 [95% CI, 0.2-0.9], respectively) infections in the first 18 years after the onset of asthma.[109] Also, the associations of asthma with the increased risk of pertussis,[50] *S pyogenes* upper respiratory tract infection,[40] and herpes zoster[91] 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 asthmatic patients includes all patients, regardless of current asthma control status or severity. This approach appears to make sense on the basis of 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 might 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 immunologic abnormalities and dysfunctions associated with atopic conditions reported in the literature are summarized in Table E1 in this article's Online Repository at www.jacionline.org. Because this is an active research area, the information in Table E1 will need to be frequently updated as new results emerge. However, the summary provides potential biological mechanisms for the epidemiologic association between atopic conditions and the increased risk of microbial infections.

Innate immunity

Innate immune dysfunction and the T_H2 immune response at the level of epithelial cells and the immune system in asthmatic patients have been well established.[115-121] The discovered mechanisms are pertinent to the increased risk of viral (eg, impaired secretion of IFN-β and IFN-λ by bronchial epithelial cells)[116,117] and bacterial (eg, impaired Toll-like receptor 2–mediated signal transduction recruiting neutrophils)[53,115] infections in patients with atopic conditions. However, impairment of innate immunity appears to occur only in a subgroup of asthmatic patients.[122] Although impaired innate immunity accounts for the association between atopic conditions and an increased risk 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 Fig E1 in this article's Online Repository at www.jacionline.org.

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 healthy control subjects found that 13 (18%) of 74 asthmatic patients and 1 (1.3%) of 74 control subjects had no response to tetanus toxoid ($P < .001$).[123] This observation was also true for atopic dermatitis (10% vs 0%, $P < .04$).[124] 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; $P = .03$).[125] This also was true for antibody responses to other vaccines. We also found that 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.[126]

Recently, we found significantly lower serotype-specific pneumococcal antibody titers in asthmatic patients than in nonasthmatic subjects (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 PBMCs after stimulation with house dust mites and the number of positive serotype-specific antibodies ($r = -0.36$, $P = .052$).[127] Lower serotype-specific pneumococcal antibody responses (IgG) were related to alleles associated with atopy and asthma (*IL4* −589T, *IL4* 2979T and *IL4RA* 551Gln) among children with recurrent otitis media aged 1 to 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, the T_H2 immune response to staphylococcal enterotoxin B was also inversely correlated with anti–pneumococcal surface protein C 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 IgG_1 titers against *Haemophilus influenzae* antigens (P4 and P6) and pneumococcal surface protein C than children without asthma or those without house dust mite sensitization at age 5 years.[132] Children with house dust mite sensitization had lower pneumococcal surface protein A titers at age 3 years. Asthmatic patients had slightly lower anti–pertussis toxin antibody levels than those without asthma.[50] T_H2 cytokines (IL-4) negatively affected antibody responses to pneumococcal polysaccharide antigens, whereas T_H1 cytokines (IFN-γ) positively affected antibody responses in an *in vivo* mouse study that assessed humoral immune response to intact *S pneumoniae*.[133,134] Our recent study showed that asthmatic children who received 1 dose of measles, mumps, and rubella (MMR) vaccine had more rapid waning of measles vaccine virus-specific IgG levels over time (a decrease of −0.114 units per year vs −0.046 units per year, $P = .01$), resulting in a lower seropositive rate than seen in those without asthma (73% vs 84%, $P = .038$). Similarly, asthmatic children subsequently had a more rapid waning of anti-measles antibody levels than nonasthmatic subjects.[135] Indeed, a previous cross-sectional study reported that a substantial percentage of asthmatic children (age, 1.6-17 years) who had received 2 doses of MMR vaccine were found to be seronegative for measles (40% to 43%) and mumps (25% to 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 control subjects (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 patients with sIgAD and 8% to 21% of patients with CVID.[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 asthmatic patients.

Cell-mediated immunity

An early study reported that 9.2% (8/87) of asthmatic children and adults and 1.2% (1/86) of subjects without asthma had no delayed-type hypersensitivity (CMI) response to any fungal, viral, and tuberculous antigens ($P < .02$, see Table E1).[123] This was also true for those with and without atopic dermatitis (45% vs 27%, $P < .001$).[124] Shirakawa et al[144] reported an inverse correlation between IgE levels and the 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. Innate and humoral immune dysfunctions alone are unlikely to fully explain the study findings on the increased risk of herpes zoster in asthmatic patients[91] 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] Patients with atopic dermatitis complicated with herpes simplex virus infection had significantly fewer IFN-γ spot-forming cells and less IFN-γ secretion by PBMCs after stimulation with herpes simplex virus than seen in control subjects, 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 the 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 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 asthmatic children 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) might increase the risk of bacterial colonization and infection in the airways of asthmatic patients.[115] However, this impairment in innate immunity alone might not be sufficient to cause certain infections, such as vaccine-preventable or invasive bacterial infections, in atopic patients. For example, opsonization of pneumococci by capsular antigen-specific antibody is a crucial mechanism for clearance of 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 Fig 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. However, a question remains about 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 might be related to T-cell or B-cell maturational development and kinetics in a manner affecting adaptive immune competence and, in turn, susceptibility to certain microbial infections.

IMPLICATIONS

Patient care

First, although clinicians and asthmatic patients need to make a concerted effort to control asthma to reduce the risk of microbial infections, asthmatic patients 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 infections (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 might be permissible for clinicians not to routinely pursue an 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 article 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 patient's humoral immunity to the 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 patients 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 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 immunologic 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 might result in a significant underestimation of the effect of asthma on morbidity and mortality and could 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 an increased risk 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 subjects. 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*–induced upper respiratory tract infection caused by asthma and other atopic conditions were estimated to be 14 (approximately 7% incidence rate difference) and 16 (approximately 6% incidence rate difference), respectively.[40,41] Although asthma and other atopic conditions only approach a 10% incidence rate difference individually (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 epidemiologic research, which better characterizes patients with atopic conditions, and laboratory research, which develops suitable immunologic assays measuring immune incompetence associated with atopic conditions, are needed because traditional immune work-ups are unlikely to reveal such immune dysfunction associated with atopic conditions.

Finally, the effects of atopic conditions or local inflammatory responses might not be limited to the airways but might be systemic. This concept is theoretically possible because 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 immunologic 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 involved in innate and adaptive immunity, at least in a subgroup of asthmatic patients. Alternatively, this subgroup of patients might not have asthma but rather an immune disorder that is 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, genome-wide 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 might have important effects on public health. This emerging research trend calls for a systematic study of the effects of asthma or other atopic conditions on a broad range of health outcomes.

Conclusions

Atopic disease ranging from mild to severe increases a person's susceptibility to various respiratory and nonrespiratory microbial infections with different degrees of effect. The effect 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 might be broader in the future. Therefore the current guidelines for asthma or other atopic conditions might need to address a broader range of management issues for infectious diseases among these patients. This review provides an insight into these foreseeable needs and challenges.

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What do we know?

- **Patients with asthma and other atopic conditions have significantly increased risks of serious and common infections with both viruses and bacteria.**
- **Atopic disease ranging from mild to severe increases a person's susceptibility to both respiratory and nonrespiratory microbial infections.**
- **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?

- **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 subjects.**
- **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.**
- **The extent to which atopic conditions affect the epidemiology of emerging and re-emerging infectious diseases at a population level is not known.**

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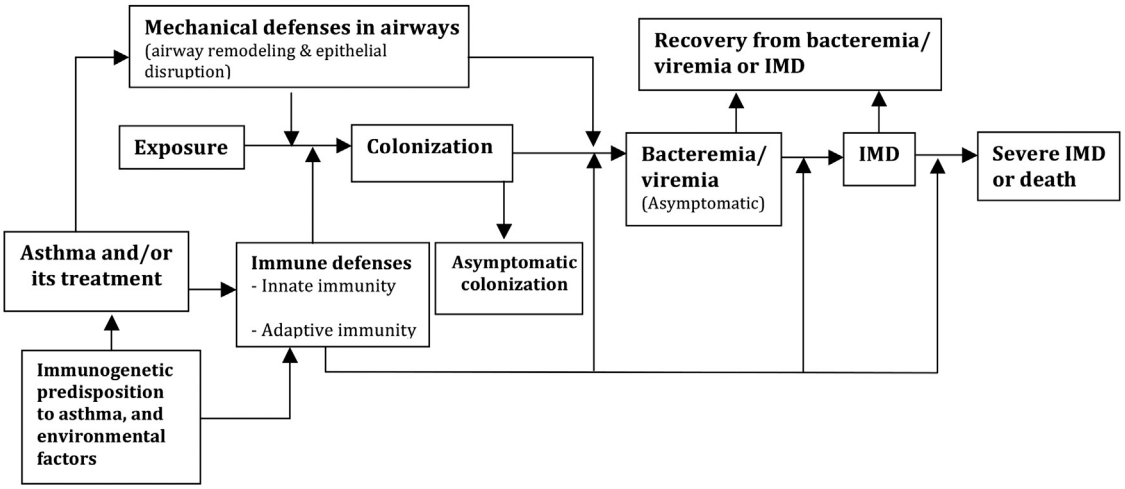

FIG E1. A conceptual proposition for the association between asthma and the risk of microbial infections. Invasive microbial disease *(IMD)* is a clinically significant infection involved in the normally sterile body fluids or organs. The figure suggests that immunogenetic predisposition to asthma and environmental risk factors and clinical asthma exert their effects on increased susceptibility to serious and common microbial infections in each stage from colonization to invasion to severe invasive microbial infection or death through alteration in the airway architecture and both innate and adaptive immune functions. This conceptual model highlights that only a subgroup of patients with immunogenetic (and environmental) predisposition to asthma, clinical asthma, or both are likely to acquire each stage of (1) colonization given the exposure, (2) asymptomatic bacteremia/viremia given the colonization or clinically unapparent infection, (3) invasive microbial disease given the asymptomatic bacteremia, and (4) severe or fatal invasive microbial disease given the invasive microbial disease. This conceptual model provides a basis for the importance of both epidemiologic research, which better characterizes patients with atopic conditions, and laboratory research, which develops suitable immunologic assays measuring immune incompetence associated with atopic conditions for early identification of such subgroups of patients with asthma or other atopic conditions to prevent the development of serious and common microbial infections.

TABLE E1. Reported immunologic abnormalities and dysfunctions associated with atopic conditions

Authors	Atopic conditions	Reported immunologic abnormalities and dysfunctions	Immune stimulants or treatment
Innate immunity			
Habibzay et al, 2012[115]	HDM-sensitized mice	• Impaired Toll-like receptor 2–mediated signaling transduction on neutrophils • Reduced neutrophil recruitment in the airways	*S pneumoniae*
Contoli et al, 2006[116]	Asthma (both steroid treated and free [human])	• Impaired IFN-λ secretion by bronchial epithelial cells in the airways	Rhinovirus
Wark et al, 2005[117]	Asthma (both steroid treated and free [human])	• Impaired IFN-β secretion by bronchial epithelial cells in the airways	Rhinovirus
Message et al, 2008[118]	Asthma (no exposure to steroid [human])	• Impaired T_H1 cytokine secretion (IFN-γ, IL-10, and IL-12) by PBMCs • Augmented T_H2 cytokine secretion (IL-4, IL-5, and IL-13) by PBMCs	Rhinovirus
Laza-Stanca et al, 2011[119]	Asthma (human)	• Impaired IL-15 secretion by epithelial cells in the airways	Rhinovirus
Plummeridge et al, 2000[120]	Asthma (human)	• Impaired IL-12 secretion by epithelial cells in the airways	LPS *(E coli)* and IFN-γ
Ho et al, 2002[121]	Asthma (all ICS-treated [human])	• Higher apoptotic susceptibility of T lymphocytes to steroid • Lower Bcl-2 expression in T lymphocytes both *ex vivo* and *in vitro* (regardless of dexamethasone treatment)	Dexamethasone
Beisswenger et al, 2006[53]	T_H2 cytokine–preincubated human bronchial epithelial cells	• Decreased antimicrobial peptide (human β-defensin 2) secretion by bronchial epithelial cells	*P aeruginosa*
	OVA-sensitized mice	• Decreased antimicrobial peptide (CRAMP) and proinflammatory cytokine (IL-1β and IL-6) secretion in the airways (BAL) • Increased T_H2 cytokine (IL-4 and IL-13) secretion in the airways and number of bacteria in the lungs (BAL)	*P aeruginosa*
Sykes et al, 2013[122]	Asthma (well controlled [human])	• No difference in rhinovirus replication or induction of IFN-β or IFN-λ secretion by epithelial cells between patients with well-controlled asthma and nonasthmatic subjects	Rhinovirus
Humoral immunity			
Grove et al, 1975[123,124]	Asthma (no steroid)/atopic dermatitis (human)	• Decreased hemagglutinin antibody response to tetanus toxoid	Tetanus toxoid vaccine
Lee et al, 1995[101]	Asthma (steroid treated [human])	• Decreased antibody level against studied polysaccharide antigens both before and after vaccination • No difference in mean fold increase	PPV23
Arkwright et al, 2000[125]	Eczema (human [moderate/severe])	• Decreased antibody level against pneumococcal vaccine (PPV23) in children aged 3-8 y but no difference in those aged 9-16 y, suggesting delayed maturation of the antibody response	PPV23
Patel et al, 2013[126]	Asthma (human)	• Decreased mumps virus–specific IgG levels with asthma	Single dose of MMR vaccine
Jung et al, 2010[127]	Asthma (human)	• Decreased serotype-specific pneumococcal antibody levels against PPV23 but not pneumococcal surface protein antibody	Pneumococcal vaccines and pneumococci
Wiertsema et al, 2007[128]	Alleles associated with atopy and asthma (human)	• *IL4* −589T, *IL4* 2979T, and *IL4RA* 551Gln associated with lower serotype-specific pneumococcal antibody responses, IgG	PCV7 followed by PPV23
Zhao et al, 2013[129]	Asthma (human)	• Inverse correlation between anti-PspC antibody levels and T_H2 immune profile (IL-5 secretion by PBMCs after stimulation with staphylococcal enterotoxin B) • Correlation modified by asthma status	PspC

(Continued)

TABLE E1. *(Continued)*

Authors	Atopic conditions	Reported immunologic abnormalities and dysfunctions	Immune stimulants or treatment
Hales et al, 2012[132]	Asthmatic or HDM-sensitized children	• Decreased IgG_1 titers against *H influenzae* antigens (P4 and P6) and PspC at age 5 y in asthmatic patients or HDM-sensitized children • Decreased PspA titers at age 3 y in HDM-sensitized children only	*H influenzae* *S pneumoniae*
Capili et al, 2012[50]	Asthma (human)	• Decreased anti–pertussis toxin antibody levels	*B pertussis*
Khan et al, 2002[133]	IL-4– or IFN-γ–deficient mice	• IL-4–deficient mice showed an increase in IgG anti-PspA response, but IFN-γ–deficient mice showed a reduced IgG anti-PspA response	Intact *S pneumoniae*
Vos et al, 2000[134]	IL-4– or IFN-γ–enhanced mice	• Persistent presence of IL-4 during B-cell stimulation suppressed T cell–independent type 2 humoral responses, which were abrogated by IFN-γ	TI-2 antigen (αδ-dex)
Yoo et al, 2014[135]	Asthma (human)	• More rapid waning of measles vaccine virus–specific IgG levels over time than in nonasthmatic subjects after 1 dose of MMR vaccination	Measles vaccine virus
Noseworthy et al, 2005[136]	Asthma (human)	• Seronegative for measles (40% to 43%) and mumps (25% to 39%)	Two doses of MMR vaccine
Urm et al, 2013[137]	Asthma (human)	• Increased risk of sIgAD/CVID	NA
CMI			
Fischer et al, 1997[62]	IL-4–overexpressing mice	• Delayed clearance of respiratory syncytial virus from the lung	RS virus
Asquith et al, 2011[81]	IL-13–deficient mice	• Decreased number of bacteria in vaginal lavage fluid	*Chlamydia muridarum*
Grove et al, 1975[123,124]	Asthma (no steroid)/atopic dermatitis (human)	• Decreased delayed-type hypersensitivity (CMI) response to any of 5 antigens (*Aspergillus fumigatus*, *Candida albicans*, mumps skin test antigen, old tuberculin, streptokinase-streptodornase)	The listed 5 antigens
Shirakawa et al, 1997[144]	IgE levels, T_H2 cytokine profiles, and atopic characteristics (human)	• Inverse association between delayed-type hypersensitivity responses to tuberculin antigens and IgE levels and risk of atopic conditions	PPD reaction
Kim et al, 2013[91]	Asthma (human)	• Increased risk of herpes zoster against which CMI has been known to be the primary defense mechanism	NA
Leung et al, 2011[147]	Atopic dermatitis complicated with herpes simplex virus (human)/IFN-γ knockout mice	• Decreased IFN-γ spot-forming cells and IFN-γ secretion by PBMCs • Disseminated viral skin infection in IFN-γ knockout mice	HSV (human PBMCs) Vaccinia virus (mice)
Schneider et al, 2010[148]	Atopic dermatitis (moderate/severe [human])	• Decreased PHA-stimulated IFN- γ SFCs • No difference in VZV-stimulated IFN-γ SFCs	VZV
Otero et al, 2013[149]	Asthma (mild [human])	• Lower production of TNF-α and IFN-γ and higher production of IL-5 by PBMCs after nonspecific stimulation with phorbol myristate acetate/ionomycin • No differences in cell-mediated immune responses after stimulating PBMCs with intact *Mycobacterium tuberculosis* and *S pneumoniae*	*M tuberculosis*, *S pneumoniae*
Yoo et al, 2010[150]	Asthmatic patients with a family history of asthma (human)	• Decreased lymphoproliferative response (MMR-specific T-cell response) to MMR vaccine virus	Two doses of MMR vaccine

BAL, Bronchoalveolar lavage; *CRAMP*, cathelin-related antimicrobial peptide; *HDM*, house dust mite; *NA*, not applicable; *OVA*, ovalbumin; *PPD*, tuberculosis skin test; *PspA*, pneumococcal surface protein A; *PspC*, pneumococcal surface protein C; *RS virus*, respiratory syncytial virus; *SFC*, sport-forming cell; *TI-2*, T cell–independent type 2; *VZV*, varicella zoster virus.