Clinical reviews in allergy and immunology

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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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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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Activity Objectives

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

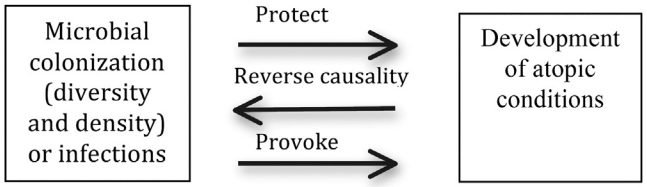

FIG 1. Relationship between microbial colonization or infections and atopic conditions. This diagram suggests a bidirectional causal relationship between exposure to microbial colonization or infection and risk of atopic conditions, which encompasses 4 specific hypotheses: the hygiene hypothesis, the 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]