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What Does Tympanostomy Tube Placement in Children Teach Us About the Association Between Atopic Conditions and Otitis Media?

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Abstract

Otitis media is the most common infection second only to viral upper respiratory infection in the outpatient setting. Tympanostomy tube insertion (TTI) is the most common ambulatory surgical procedure in the United States. While many risk factors for otitis media have been identified, atopic conditions have been under-recognized as risk factors for recurrent and persistent otitis media. Given that asthma and other atopic conditions are the most common chronic conditions during childhood, it is worth examining the association between atopic conditions and risk of otitis media, which can provide insight into how atopic conditions influence the risk of microbial infections. This paper focuses its discussion on otitis media, however it is important that the association between atopic conditions and risk of otitis media be interpreted in the context of the association of atopic conditions with increased risks of various microbial infections.

Keywords

Tympanostomy tube; Children; Pediatrics; Otitis media; Adaptive immunity; Allergic rhinitis; Asthma; Atopic dermatitis; Epidemiology; Immune dysfunction; Immune incompetence; Infection; Innate immunity; Phenotype; Risk; Susceptibility

Introduction

Otitis media is defined as inflammation of the middle ear. According to the 2013 otolaryngology practice guidelines, recurrent acute otitis media (with three or more separately documented acute otitis media cases in the past six months or at least four separately documented acute otitis media cases in the past 12 months) with middle ear

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Compliance with Ethics Guidelines

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effusion or persistent otitis media with effusion >3 months are recommended to receive tympanostomy tube insertion (TTI) in children.[1] Otitis media causes a significant burden to society and TTI is the most common ambulatory surgery performed on children in the United States.[1] Approximately half of all children were reported to have three or more episodes of acute otitis media by three years of age.[2] About 7% of U.S. children had tubes inserted by three years of age and 20% of patients who underwent initial placement of bilateral tympanostomy tube required a second set of ventilation tubes.[3-5]

Although the introduction of the pneumococcal conjugate vaccine in 2000 reduced the incidence of otitis media, or as proxy, reduced the frequency of otitis media-caused health care visits,[6-9] serotypes not covered by vaccine continue to cause a significant proportion of otitis media in the post-vaccine era.[10,11] The 2009 Medical Expenditure Panel Survey data showed that one in ten children (age<18 years) per year is diagnosed with acute otitis media in the U.S. This phenomenon manifests in an additional 2.0 office visits, 0.2 emergency department visits, and 1.6 prescription fills (all $P<.001$) per year as compared to those without acute otitis media.[12] Overall, otitis media causes significant social and financial burden to families of young children, accounting for more than 16 million office visits a year at an annual cost of more than $4 billion (2003) in the U. S. alone.[13,14]

The known risk factors for recurrent otitis media include: age (peak in 6-18 months),[15] male,[2,16,17] ethnicity (Caucasian),[16,18,19] exposure to smoking, [17,20-28] breastfeeding,[21,25,29-33] daycare attendance,[16,21-23,25,33-35] low socioeconomic status, [17,22,36] and a family history of otitis media.[20,25,34,35,37] The risk factors associated with otitis media suggest similar patterns of association with risk of asthma except ethnicity. We could not find any paper identifying inhaled corticosteroid or systemic corticosteroid as a risk factor of recurrent otitis media. Steroid use might play a role in the association between atopic conditions and the risk of ear infections, a hypothesis we will discuss later in the article.

In our review, we discuss asthma and other atopic conditions as relatively under-recognized risk factors for otitis media. In this respect, asthma and other atopic conditions have clinical and public health significance since they affect a large proportion of children in the United States. Asthma is the most common chronic illness in childhood and a major cause of morbidity in adults. Asthma affects 4-17% of children, 7-13% of adults and is one of the five most burdensome chronic diseases in the U.S..[38-42] The prevalence of atopic dermatitis (10-19%) [43-45] and allergic rhinitis (26 to 33%)[43-46] in the U.S. population is similar to or even greater than that of asthma. Therefore, asthma and other atopic conditions affect a significant proportion of people in the U.S. While atopic condition-related morbidity (e.g., poorly controlled asthma) has been widely studied, little is known about the extent to which morbidity resulting from the increased risk of microbial infections (e.g., otitis media) associated with atopic conditions impacts our society.

Therefore, since otitis media is the most common bacterial infection and atopic conditions collectively are the most common chronic condition during childhood, it is worth examining the nature of the association between them. In this paper, we will discuss the following topics: 1) the association of atopic conditions with an increased risk of otitis media, 2)

consideration of pertinent factors related to the association, 3) potential mechanisms underlying the association, and 4) implications on clinical practice, research, and public health.

1. Atopic Conditions and Risk of Otitis Media

Although eosinophilic otitis media has been previously described,[47] given the scope of this review paper, here we shall discuss the association between atopic conditions and the risk of bacterial otitis media without differentiating between the types of otitis media (i.e., acute otitis media, otitis media with effusion, and chronic suppurative otitis media). The literature on the association between atopic conditions and the risk of otitis media is summarized in Table 1. Most studies were observational, and cross-sectional. Although the associations appear to be inconsistent depending on the differences of the study design and population, overall, asthma and allergic rhinitis appear to have stronger association with the risk of ear infection as compared to atopic dermatitis, which shows a weak association.

Some of the inconsistency on the association between atopic conditions and risk of otitis media is stemming from inconsistent definition of exposure and outcome measures for the association. For example, a study by Umapathy, et al. uses a scoring system of symptoms related to allergic diseases and ear infection (0: absence; 1-5:possible; ≥6: strong),[48] whereas, a study by Kraemer, et al. uses frequency of atopy symptoms per month to suggest that asthma (or other atopic diseases) severity might associate with the risk of ear infection.[20] In addition, some studies required a strict definition of atopic conditions (e.g, allergic rhinitis requiring a positive skin prick test and concurrent allergic symptoms)[49] and others often had homogenous or special populations limiting generalizability.[30] There were two longitudinal studies: one of which was a prospective study showing the association of acute otitis media in 10-year-olds with atopic eczema during the first 6 months of life using a birth cohort,[27] the other was a retrospective cohort study in which our group assessed the relationship between asthma and other atopic conditions and TTI as a surrogate marker for recurrent or persistent otitis media according to recent otolaryngology guidelines.[1]

Bentdal, et al. conducted a prospective cohort study in Norway which compared the incidence of otitis media among children with and without early life atopic eczema by following for 10 years since birth. History of early life atopic eczema, which was defined as having atopic eczema the first 6 months of life, was taken from questionnaires at 6 and 12 months. Of the 2,344 children whose parents reported the status of early life atopic eczema, 385 (16.4%) had early life atopic eczema. They found that early life atopic eczema was significantly associated with risk of otitis media at 10 years of age (adjusted OR:1.4, 95%CI: 1.0-1.9) adjusting for gender, parental smoking, maternal education, parental atopy, child care attendance, breastfeeding, older siblings, otitis media surgery and early acute otitis media.[27] In this study, the risk of acute otitis media in later age was more strongly associated with atopic eczema compared to that in the first year of life. The authors suggested that early acute otitis media may be a result of an immature immune system and anatomically dysfunctional Eustachian tubes.[50,51] Alternatively, immunogenetic predisposition to atopic eczema might contribute to the risk of ear infection.

In our study, there was little evidence for over-utilization of TTI. About 7% of children in the U.S. undergo TTI during early childhood,[52] and similarly, in our study, nearly 6% of children had undergone TTI. We chose to examine the relationship between atopic conditions and the incidence of TTI. We determined asthma and atopic condition status independent of data collection of TTI to minimize observation bias. Children with asthma (RR: 1.53, 95% CI: 0.93-2.53) or other atopic conditions (RR: 1.70, 95%CI:1.01-2.86) had higher incidence rates of TTI than non-asthmatics.[17] The effect size of the association in our study appears to be similar to that in the prospective study by Bentdal, et al discussed above. If we limit the analysis to asthma or atopic conditions only prior to index date of TTI, the association was much stronger but the analysis was limited by a small sample size.

Given the incidence of TTI among healthy children without asthma (4.4 per 1,000 person-years) or other atopic conditions (4.7 per 1,000 person-years), attributable risks for TTI due to asthma (6.7 per 1,000 person-years) or other atopic conditions (7.3 per 1,000 person-years) were estimated to be 34% and 36%, respectively. These estimated attributable risks suggest that the significant number of TTI could be attributable to atopic conditions. Taken together, atopic conditions have shown to be associated with an increased risk of otitis media. This finding raises a question: is this association also true for other infections caused by *Streptococcus. pneumonia*, such as invasive pneumococcal disease or community-acquired pneumonia? If so, knowing this relationship may help to address causal inference in terms of consistency and coherence as discussed below.

2. Atopic Conditions and Risk of other Pneumococcal Diseases

Given the association between atopic conditions and the risk of otitis media, it is important to examine the relationship between atopic conditions and the risks of *other* pneumococcal infections. Previous studies have shown that asthma is associated with increased colonization with *S. pneumoniae* in the nasopharynx.[53-55] In addition to nasopharyngeal colonization, asthma has been shown to increase the risk of invasive pneumococcal disease (IPD) and pneumococcal pneumonia in patients with asthma as compared to those without asthma.[56-59] The population attributable risk percent (PAR%) for asthma in these serious pneumococcal diseases was about 11-17%. A recent systematic review concluded that the risk of IPD increased among individuals with asthma.[60] The U.S. Advisory Committee of Immunization Practices (ACIP) now recommends a single dose of 23-valent polysaccharide pneumococcal vaccine (PPV23) to individuals with asthma ages 19-64 years in 2008.[61] Also, we reported significantly increased risk of IPD and/or pneumococcal pneumonia among individuals with atopic dermatitis and/or allergic rhinitis as compared to those without such conditions and importantly, this association was independent of asthma status (adjusted odds ratio, 2.13; 95% CI, 1.04-4.35).[62]

Therefore, the impact of atopic conditions does not seem to be limited to otitis media but extends to influence risk for invasive pneumococcal disease/pneumonia as well. This conclusion sheds light into the conceptual framework of the relationship between atopic conditions and microbial infections in general, which currently considers: 1) microbial colonization or infections reducing the risk of atopic conditions reflected in the ‘hygiene hypothesis’,[63,64] 2) microbial exposure rather increasing risk of atopic conditions (e.g.,

rhino virus or bacterial colonization),[65,66] 3) contextual influences of microbial exposure on risk of atopic conditions (e.g., the microbiome hypothesis),[67,68] and 4) atopic conditions (or immunogenetic predisposition to atopic conditions) increase risk of microbial colonization or infection reflected in 'reverse causality'.[17,57,62,69] Discussing each theoretical proposition is beyond the scope of this paper. But, the literature pertaining to the association of atopic conditions with the increased risk of otitis media and other infections seems to support 'reverse causality'.

3. Factors in the Relationship Between Atopic Conditions and the Risk of Microbial Infection

Although there are many potential factors involved in the relationship, we focus this discussion on: 1) corticosteroid therapies, 2) the temporal relationship between atopic conditions and the risk of infection or colonization and 3) detection bias.

3-1. The Influence of Corticosteroid Therapies on the Risk of Infection

Little is known about the role of inhaled corticosteroids (ICS) in the risk of otitis media. ICS therapy has not been reported to be associated with the risk of developing pneumonia as an adverse event among asthmatics (hazard ratio, HR: 1.29, 95%CI: 0.53-3.12). In fact, ICS reduces the risk of pneumonia as a serious adverse event among asthmatics (HR: 0.52, 95%CI:0.36-0.76) based on pooling a number of clinical trials.[70] This association was independent of the dose, type, and duration of ICS. Another study reported that oral corticosteroid therapy among patients using vitamin D resulted in a reduced risk of pneumonia.[71] Also, it has been found that ICS does not account for the association of atopic conditions with risks of various microbial infections[577273,7475,7656] Systemic corticosteroid therapy does not influence humoral or cell-mediated responses to vaccines or increase the risk of clinical infection.[77-81]

Little is known about the role of asthma control status and the severity of risk for otitis media. However, the literature suggests that low-risk asthma still poses an increased risk of invasive pneumococcal diseases.[5658] Whether this is true for otitis media is unknown. Future studies need to address this issue. In summary, corticosteroid therapies are unlikely to account for the association of asthma/other atopic conditions with the increased risk of otitis media.

3-2. Temporal Relationship Between Atopic Conditions and Infection

When does the impact of asthma or other atopic conditions on the increased risk of otitis media begin? It is challenging to address this question since the temporality is difficult to discern and because otitis media typically occurs during infancy and early in childhood. However, recent studies do shed light into this area. Bisgaard, et al. reported colonization with certain bacteria (*S. pneumonia, H. influenza*, and *M. catarrhalis*, not *S. aureus*) during the newborn period was associated with subsequent development of asthma at five years of age.[66] The results can be interpreted bi-directionally in the causal relationship. The same group reported that children who develop asthma by age seven (14%) have a significant airflow deficit as newborns (forced expiratory flow at 50% of vital capacity/second in

newborns reduced by 0.34 z score; *P*=.03)[82] using the same birth cohort for the association between bacterial colonization during a neonatal period and the development of asthma. Their results might support "the hypothesis of early programming of asthma" and have been supported by other studies.[83-86] Overall, these results suggest that the inception of the characteristics of asthma, such as the impairment of lung function, begins even before one develops asthma-like symptoms like wheezing. Further, colonization with certain bacteria might be an important but not well-recognized predictive feature for childhood asthma. The study by Bisgaard, et al. could not observe the association between bacterial colonization at twelve months of age and development of asthma at five years of age based on a multivariate model.[66] However, the study did not examine the relationship between change or persistence of bacterial colonization during the first twelve months of life and development of persistent wheezing. Given the collinearity with bacterial colonization during a neonatal period and the relatively short duration of bacterial colonization (e.g., 29-51 days for pneumococci[8788]) and high acquisition rates (e.g., 0.012 per person-month for pneumococci[89]), it may be important to determine the association between changes in bacterial colonization over time, subsequent asthma status and the risk of infection before and after the onset of asthma.

Our group assessed the risk of *Streptococcus. pyogenes* upper respiratory infection before and after the index date of asthma (when one meets the criteria for predetermined asthma criteria).[73] While patients with asthma had a higher incidence rate of *S. pyogenes* infection than nonasthmatics (0.25 per person-year vs. 0.18, adjusted RR: 1.40, 95%CI: 1.12-1.74), there was *no difference* in the incidence rate of *S. pyogenes* infection before (0.29 per person-year) and after the index date of asthma (0.24 per person-year, *P*=.17). This finding was independent of the incidence of the tests (e.g., PCR) for *S. pyogenes* (0.93 vs. 0.87, respectively, *P*=.52). Also, the incidence of the tests for *S. pyogenes* did not differ by physician diagnosis of asthma suggesting our study findings were unlikely to be influenced by a detection bias. We replicated these findings with the incidence of TTI, a proxy measure for persistent or recurrent otitis media.[17] Asthma was associated with an increased risk of TTI (RR: 1.93 to 19.3) but there was no difference in the incidence of TTI before (7.3 per 1000 person-year) and after the index date of asthma (6.1 per person-year, *P*=.55). However, these study findings were based on small sample sizes and need to be replicated in future studies with a larger sample size. Regardless, they might be consistent with the study findings reported by Bisgaard, et al.

Taken together, the asthma-related increased risk of otitis media or other infections or colonization may precede the development of asthma symptoms or the onset of clinical asthma suggesting that the preceding microbial colonization or infections might be an important feature of the ensuing atopic conditions. Alternatively, otitis media and other infections/colonization in the early airways might have some causal relationship in the development of asthma. Future studies need to address the temporality of this relationship by conducting prospective cohort studies.

3-3. Detection Bias

Detection bias in epidemiology arises when exposure status causes a differential probability of detecting outcomes. For example, if parents of asthmatic children might be more likely to seek medical evaluations or testing than parents of children who are non-asthmatic or those without atopic conditions, this might result in an increased detection of outcomes (e.g., infections or positive tests) among children with asthma or other atopic conditions compared to those without such conditions. The influences of exposure status on the likelihood of detection of outcomes can stem from patients (or caregivers/guardians for children), clinicians and other factors (e.g., health care system or community).

For our study findings on the association between asthma and an increased risk of TTI, we assessed the incidence of TTI before and after physician diagnosis of asthma and we found no significant difference (8.0 vs. 7.2 per 1,000 person-years, P=.73).[17] To assess whether parents of children with asthma are more likely to seek medical evaluations for mild acute illnesses, we compared the correlation between the frequency of acute illnesses and that of medical visits between young children with asthma and those without asthma aged two years (standard deviation: 1.0 year). In our study setting, we found no difference in the likelihood of parents who seek medical evaluations for children with asthma and those without asthma (rho=0.62 vs. rho=0.64).[90] In our follow-up study, the mean proportions of medical evaluation per acute illness of asthmatic and non-asthmatic subjects were 41% and 39%, respectively (P=.75). Also, the mean frequency of medical evaluation per acute illness per year of asthmatic and non-asthmatic subjects were 6.5% and 7.5%, respectively (P=.55).[91] In addition, a physician diagnosis of asthma before versus after did not make a difference in the incidence of *S. pyogenes* testing (0.92 vs. 0.89 per person-year, P=.75).[73] This was true for children with and without other atopic conditions (0.87 vs. 0.83, respectively P=.61).[92]

We also assessed the likelihood of differential diagnostic testing and treatment for children with a physician diagnosis of asthma by clinicians.[93] We compared the frequency of chest x-ray and antibiotic therapies by clinicians between children with and without a physician diagnosis of asthma among children who met the criteria for asthma. We found that a physician diagnosis of asthma made no significant difference in the likelihood of requesting a chest x-ray (6.2% vs. 4.9%, respectively P=.44) or ordering antibiotic treatments (7.6% vs. 4.7%, respectively, P=.096).

4. The Potential Mechanisms

Although Eustachian tube dysfunction due to temporary (e.g., URI) or persistent (e.g., cleft palate) structural abnormality is a major preceding step for acute otitis media, this section focuses on immune mechanisms underlying the increased risk of otitis media among children with atopic conditions. As *S. pneumoniae* and non-typeable *H. influenza* are the two most common organisms causing otitis media, this paper will focus its discussion on the underlying mechanisms of 1) innate immunity, 2) humoral immunity and 3) cell-mediated immunity involving these two organisms.

4-1. Innate Immunity

Impairment in innate immunity in asthmatics at the level of epithelial cells and immune system has been widely studied.[94-101] Although this paper did not discuss the association between asthma and risk of viral infections, the impairment in innate immunity is pertinent to the increased risk of viral infection in the airways (e.g., impaired secretion of IFN-β and λ by bronchial epithelial cells) which is an important risk factor for otitis media.[96,97] More specifically, recent studies showed that allergic sensitization (e.g, house-dust mite) resulted in impairment in innate immunity which in turn, increased risk of pneumococcal infection (e.g., impaired TLR-2 mediated signal transduction recruiting neutrophils).[94,102] Therefore, impaired innate immunity plays an important role in accounting for the association between atopic conditions and an increased risk of otitis media.

4-2. Humoral Immunity

Impairment in adaptive immunity is likely to contribute to increased susceptibility to otitis media among patients with atopic conditions because pneumococcal serotype-specific antibodies provide protection against otitis media.[103,104] Although atopic conditions are associated with an increased risk of otitis media, little is known about which specific humoral immune functions are impaired, thereby increasing the risk of otitis media in children with asthma or other atopic conditions. However, since pathogen-specific humoral immunity is impaired in children with recurrent otitis media, this could be a potential mechanism for the association between atopic conditions and an increased risk of otitis media.

For example, Sharma, et al. showed that otitis media-prone children had significantly lower percentages of memory B cells to pneumococcal protein antigens and also had reduced antigen-specific IgG levels after nasopharyngeal infection or colonization with *S. pneumoniae* than non-otitis media-prone children.[103] Kaur, et al. showed similar findings with non-typeable *H. influenza*.[104] Although it is unknown whether children with atopic conditions have impaired humoral immunity, it can be postulated that otitis media prone-children with humoral immune dysfunction might be over-represented in children with atopic conditions as discussed below.

A previous study looked at tetanus toxoid-specific humoral immunity in asthmatic patients (who were not on steroids) and healthy individuals and found that 13 of 74 asthmatic patients (18%) failed to respond to tetanus toxoid compared to 1 of 74 normal individuals (1.3%) ($P<.001$).[105] This was also true for atopic dermatitis (10% vs. 0%, $P<.04$).[106] Another study compared serotype-specific pneumococcal antibody levels before and after vaccination with PPV23 between children with asthma and those without asthma aged 2-18 years.[78] Asthmatics had significantly lower antibody levels against the studied pneumococcal antigens both pre- and post-vaccination. Another study assessed antibody response to PPV23 in children with and without atopic dermatitis aged 3-8 years and found that 17% of children with atopic dermatitis responded to PPV23, compared to 57% of children without atopic dermatitis (OR:0.2, 95%CI: 0.05-0.84, $P=.03$).[107] This was true for antibody responses to other vaccines. We recently reported significantly lower serotype-specific pneumococcal antibody levels in individuals with asthma as compared to those

without asthma (8.5 and 15.5 of 23 serotypes, respectively, *P*=.034). We also found an inverse relationship between the ratio of IL-5/ IFN-γ secretion by PBMC after stimulation with house-dust mite and the number of positive serotype-specific antibodies (r= − 0.36, *P*=.052).[95] Lower antibody responses were observed for alleles previously associated with atopy, IL-4 -589T, IL-4 2979T and IL-4 Ralpha 551Gln.[108] Several mouse and human studies have showed that asthma status, house-dust mite sensitization, and Th2 cytokines impair humoral immune responses to *S. pneumoniae*, *H. influenza*, and *B. pertussis*.[109-112]

We recently reported the association between asthma and selective IgA deficiency/common variable immune deficiency (CVID).[113] A history of asthma before the incidence date of selective IgA deficiency/CVID (OR: 2.77; 95% CI, 1.09-7.06) was more prevalent in sIgAD/CVID cases than in their matched controls (OR: 3.57; 95% CI, 1.50-8.51). These results potentially suggest asthma, or the associated immune mechanisms, might influence the maturation of B cells into immunoglobulin-producing plasma cells (e.g., isotype switching defect or post-switch defect).[114-116] The literature suggests that TNFRSF13B gene (TACI gene-transmembrane activator and calcium-modulator and cyclophilin ligand interactor) mutations account for 6.25% of sIgAD and 8-21% of CVID patients.[117,118] A recent Swedish study showed that children with TNFRSF13B mutations had a 2.5-fold increased risk of asthma at four years of age independent of IgE levels.[119] These study findings all shed light into potential humoral immune dysfunctions in asthmatics.

4-3. Cell-mediated Immunity

Recent studies showed that cell-mediated immunity is impaired in children with recurrent otitis media.[120] Cell-mediated immunity is also important for host defense against bacterial infection. Malley, et al. reported that sustainable immunity to pneumococcal colonization could be induced in the absence of pneumococcal antibody, independent of the capsular polysaccharide antigens. This protection required the presence of CD4(+) T cells at the time of challenge suggesting an important role of cell-mediated immunity against pneumococcal infection.[121] Few studies assessed the specific impairment in cell-mediated immunity responsible for the increased risk of otitis media among children with atopic conditions. Burnstein, et al. reported that lymphocytes from the adenoids showed decreased Th1 cytokines (IL-2 and IFN-γ) but normal Th2 cytokine (IL-4 and IL-5) secretions after stimulation with phytohemagglutinin than lymphocytes from PBMC among children with recurrent otitis media, suggesting the underlying immune profile associated with atopy might play a role in determining the risk of recurrent otitis media.[122]

Previous studies have showed that individuals with asthma (9.2% vs. 1.2%, P<.02) or atopic dermatitis (45% vs. 27%, P<.001) fail to mount tetanus toxoid-specific cell-mediated immunity compared to healthy individuals.[105106] An inverse correlation between IgE levels and the size of tuberculin response, as a marker for cell-mediated immunity (CMI) has been reported, suggesting a potential negative influence of atopic status on CMI.[123] Asthma and atopic dermatitis have been associated with impaired CMI after non-specific stimulation in patients with asthma or atopic dermatitis but antigen-specific CMI was not impaired.[124,125] We recently reported that asthmatic children with a family history of asthma aged 12-18 years who had received two doses of the MMR vaccine had significantly poorer CMI

responses to MMR vaccine viruses than non-asthmatics.[126] An unpublished cross-sectional study showed that a significant proportion of asthmatics aged 1.6-17 years, who had received two doses of MMR, became seronegative for measles (40-43%) and mumps (25-39%) immunity.[127]

Taken together, impairment in both innate and adaptive immunity against pneumococci and non-typeable *H. influenza* might increase the risk of bacterial colonization and infection in the pediatric airway. Also, immune incompetence in children with atopic conditions increases the risk of IPD and pneumococcal pneumonia. A question remains as to why some atopic patients develop asthma and others not. Immunogenetic mechanisms associated with atopic conditions might be related to T cell or B cell maturation and kinetics in a way that results in adaptive immune incompetence and susceptibility to pneumococcal infections including otitis media.

5. Relevance and Implications

5-1. Clinical practice

Irrespective of atopic conditions, clinicians and parents of children with frequent and persistent ear infections should make every effort to reduce exposures to modifiable risk factors such as cigarette smoking, both at home and in cars. For the specific issues related to atopic conditions, first, given the increased risks of otitis media among children with atopic conditions, clinicians might perform more careful clinical and laboratory evaluations for those with recurrent or persistent otitis media to discern whether a patient has undiagnosed asthma or other atopic conditions instead of solely seeking primary immunodeficiency. If a patient has atopic conditions, clinicians may consider an immune deficiency work-up including immunoglobulin levels (IgG, IgA, and IgM) given the potential association of asthma with selective IgA deficiency and CVID which are the two most common primary immunodeficiency disorders. The information discussed in this paper might be useful for clinicians in counseling otherwise healthy asthmatic or atopic children with normal immune functions who are concerned about the increased risk of recurrent or persistent otitis media.

Second, the role of antibiotic therapy or prophylaxis for atopic patients with recurrent or persistent otitis media needs to be studied in terms of the risks and benefits of various approaches. A previous study reported that otitis media was significantly reduced by 75% in the sulfisoxazole group, 38% in the pneumococcal vaccine group and 90% in the group treated with both agents. The latter group also reduced acute asthma exacerbation by 56% and decreased hospitalizations associated with otitis media by 90%.[128] Given the large proportion of children affected by atopic conditions at a population level, individualized guidelines for antibiotic prophylaxis or early ENT referral and TTI for high-risk children for otitis media should be considered.

Third, given the significantly increased risk of various microbial infections other than otitis media,[69] it is important for both clinicians and patients with atopic conditions to follow the guidelines of all routine vaccinations as discussed in this paper (e.g., pertussis).[129] This is especially true for the influenza vaccine given the low influenza vaccine uptake rate (40%)[130,131] and higher risk and severity of influenza in individuals with asthma and other

atopic conditions. Clinicians and professional organizations concerning individuals with asthma and other atopic conditions should develop strategies to improve influenza vaccine uptake rate. Along these lines, both clinicians and patients with asthma need to be aware that people with asthma aged 19-64 years should be vaccinated with a single dose of PPV23. The current ACIP recommendation does not limit pneumococcal vaccinations (PPV23) to only severe asthmatics or those with poorly controlled asthma given the increased risk of IPD among people with mild asthma.

5-2. Research

Going forward it will be important to assess whether children with atopic conditions have the aforementioned adaptive immune dysfunctions observed in children with recurrent otitis media. This will improve our current understanding of why children with asthma or other atopic conditions have an increased risk of otitis media beyond Eustachian tube dysfunction and this knowledge can be applied to the relationship between atopic conditions and risk of other infections.

It is likely that a subgroup of children with atopic conditions have an increased risk of recurrent or persistent otitis media due to underlying immune incompetence. However, it is unknown which patients with asthma or other atopic conditions are more susceptible to serious or common microbial infections than others. Given the significant attributable risks of asthma and other atopic conditions for TTI (34% and 36%, respectively), a significant number of TTI in children are attributable to atopic conditions. Thus, it will be important to develop a strategy (clinical and laboratory approaches) to identify a subgroup of children with atopic conditions who have an increased risk of recurrent or persistent otitis media and underlying immune incompetence. To meet this goal, the coordinated efforts of epidemiological research, to better characterize patients with atopic conditions, and laboratory research, to develop suitable immunological biomarkers measuring immune incompetence associated with atopic conditions, are indispensible.

Finally, to better characterize asthma in terms of phenotypes or endotypes, it will be necessary to consider including both: 1) susceptibility to serious and common microbial infections and 2) measurable immune incompetence into the currently recommended predictors and outcome variables for asthma research. The current recommendations do not include risk of microbial infection and immune incompetence in asthma research.[132133-139] In this respect, a history of recurrent or persistent otitis media (or TTI) might be a suitable and feasible outcome of atopic conditions to be considered.

5-3. Public Health

Given the impact of atopic conditions on the risk of otitis media as well as the increased likelihood of exposure to antibiotics, it will be important to involve public health surveillance for the epidemiology of pneumococcal and other bacterial organisms responsible for otitis media among children with atopic conditions. Little is known about the extent to which atopic conditions contribute to antibiotic resistance to *S. pneumoniae* and serotype shifting of pneumococci due to differential inadequate immune responses to certain pneumococcal serotypes.[108,140] In this respect, it will be prudent to monitor pneumococcal

serotypes and their bacterial characteristics in children with or without atopic conditions who undergo TTI at a community level.

Conclusions

Children with asthma or other atopic conditions have a significantly increased risk of recurrent or persistent otitis media. Children with immunogenetic predisposition to asthma or atopic conditions appear to have a similar risk for otitis media even before the onset of clinical asthma. This association is unlikely to be due to asthma medications or detection bias but potentially due to impairment in both innate and adaptive immunity and structural alterations of upper airways. Given the significant impact of atopic conditions on the risk of recurrent and persistent otitis media and the large proportion of children who are affected by atopic conditions, it is necessary to develop individualized guidelines for the management of recurrent or persistent otitis media for children with atopic conditions, a relatively under-recognized risk factor for otitis media. Also, it is reasonable to believe that increased susceptibility to otitis media linked to underlying immune dysfunctions is a potential feature of atopic conditions. In the future, the guidelines for management of asthma or other atopic conditions should consider addressing a broader range of management issues for infectious diseases including recurrent and persistent otitis media among patients with atopic conditions.

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Abbreviations

95%CI	95% confidence interval
CMI	cell-mediated immunity
CVID	common variable immunodeficiency
HIV	human immunodeficiency virus
HR	hazard ratios
ICS	inhaled corticosteroid
IPD	Invasive pneumococcal disease
OR	odds ratios
PAR%	population attributable risk percent
PBMC	peripheral blood mononuclear cells
PCV7	7-valent pneumococcal conjugate vaccine
PPV23	23-valent pneumococcal polysaccharide vaccine
RR	risk ratios

Th1	T-helper 1 cells
Th2	T-helper 2 cells

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Table 1

Summary of the literature on the association between atopic conditions and risk of otitis media

Authors / Design	Subjects	Outcome	Exposure	Result
Bentdal, population-based prospective cohort (Norway)[27]	N=3,754 (birth cohort)	Incidence of AOM[#] at age 10	Incidence of early life (first 6 months of life) eczema (16%)	Early life atopic eczema, aOR=1.4(1.0-1.9)
Bjur, retrospective cohort (US)[17]	N=320 community sample of children	Incidence of TTI[*](0-18years)	Incidence of asthma by criteria, physician diagnosis of AR/AD	1. Asthma, RR= 1.53(0.93-2.53) 2. AR[¶] and/AD[†], RR= 1.70 (1.01-2.86)
Marseglia, hospital-based cross-sectional (Italy)[141]	N=287 patients with acute URI for ≥ 10 days (age 2-15 years)	Prevalence of OME[^]	Prevalence of AR (SPT[+] plus physician-diagnosis)	AR, aOR=2.53 (1.25-5.11)
Umapathy, community-based cross-sectional (UK)[48]	N=253 primary school children (age 5-6.5 years)	Scores of OME symptoms	Scores of asthma and allergic rhinitis symptoms	1. Asthma, positive association (P<.0001) [##] 2. Rhinitis, positive association (P<.0001) [##]
Bentdal, population-based cross-sectional (Norway)[142]	N=3,406 (birth cohort, studied at age 10 years)	Incidence of AOM at age 10	Asthma/AR/AD (physician-diagnosis(ever) plus 12-month prevalence of related-symptoms)	1. Asthma, OR=2.7 (1.8-4.0) 2. AR, OR=1.3 (1.0-1.9) 3. AD, OR=1.5 (1.1-2.1)
Chantzi, hospital based cross-sectional (Greece)[35]	N=168 ENT patients (age 1-7 years)	Prevalence of OME	Prevalence of wheezing/nasal obstruction/eczema	1. Wheezing, aOR=8.17 (2.68-24.92) 2. Nasal obstruction, aOR=2.84 (0.96-8.36) 3. Eczema, aOR="nonsignificant"
Chen, community-based cross-sectional (Taiwan)[143]	N=8,012 from 3 junior high schools (age 10-18)	12-month prevalence of OM (by report)	12-month prevalence of allergic disease symptoms	1. Asthma, OR=0.67 (0.21-2.12) 2. AR, OR=1.91 (1.51-2.43) 3. AD, OR=1.61 (0.78-3.35)
Grupp-Phelan, population-based cross-sectional(US)[144]	N=71,818 from GHC[††] in 1992 (age 1-17)	3 or more visits for OM in 1992	Prevalence of asthma (by ICD-9 code)	Asthma, OR=1.8 (1.6-1.9)
Savini, cross-sectional(Italy)[145]	N=372 (age 4-14); 172 hospital patients with OME and 200 local school students without OME	Prevalence of OME	Prevalence of asthma, AR, AD (symptom-based questionnaires)	1. Asthma, OR=1.4(0.61-3.22) 2. AR, OR=3.72(0.98-38.12) 3. AD, OR=2.6(1.16-5.99)
Kraemer, hospital-based cross-sectional (US)[20]	N=152; 76 TTI(mean age 3.52), and 76 non-TTI (3.37) having other surgery	Prevalence of TTI	12-month prevalence of nasal congestion, and atopy (defined as one or more asthma-, AR-, or AD-related symptoms)	1. Frequency of nasal congestion (days/month) a. 1-5: RR=3.0 (1.0-8.8) b. 6-15: RR=4.6 (1.7-12.8) 2. Frequency of atopy (days/month) a. 1-15: RR=1.4 (0.4-4.5) b. >15: RR=3.7 (1.3-10.6)
Souter, cross-sectional (New Zealand)[146]	N=3,630 (age 6-7); 89 TTI hospital patients, and 3,541 reference group participated in the ISAAC study	Prevalence of TTI	12-month prevalence of allergic symptoms, rhinoconjunctivitis (nasal symptoms PLUS current watery or itchy eyes), eczema	1. Wheeze, OR=1.14 (0.70-1.85) 2. Nasal symptoms, OR=2.01 (1.30-3.10) 3. Rhinoconjunctivitis, OR=1.14 (0.60-2.16) 4. Eczema, OR=0.76 (0.39-1.47)
Yeo, hospital-based cross-sectional (S. Korea)[49]	N=264 (age<15); 123 TTI and 141 non-TTI having other surgery	Prevalence of TTI	Prevalence of AR (SPT plus concurrent symptoms)	AR, 28.4% (TTI) vs. 24.1% (non-TTI), P>.05
Saim, community-based cross-sectional (Malaysia)[30]	N=1,097 preschool children (age 5-6)	Prevalence of OME	Prevalence of asthma on treatment & allergy (questionnaire)	1. Asthma on treatment, no association, P=.98 2. Allergy, no association, P=.1

[*] TTI: Tympanostomy tube insertion;

[¶] AR: allergic rhinitis;

[†] AD: allergic dermatitis;

[^] OME: otitis media with effusion;

[+] SPT: skin prick test;

[#] AOM: acute otitis media;

[##] The paper did not report parameter estimates;

[††] GHC:Group Health Cooperative