Influence of Asthma Epidemiology on the Risk for Other Diseases

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Asthma is a multifactorial chronic disease affecting a significant proportion of people in the United States and worldwide. Numerous laboratory and epidemiological studies have attempted to understand the etiology and underlying mechanisms of asthma and to identify effective therapies. However, the impact of asthma on the risk for other diseases has drawn little attention. This paper discusses the potential effects of asthma as a risk factor for other diseases, explores the potential mechanisms, and reviews the implications of the findings to clinical practice, public health, and research.

Key Words: Asthma; epidemiology; population; chronic diseases; risk; susceptibility

INTRODUCTION

Asthma is a reversible and variable airflow obstruction caused by chronic airway inflammation. Numerous laboratory and epidemiological studies have focused on the etiology and mechanistic pathways of asthma, in order to improve diagnosis, therapy, and prognosis. Although these efforts have significantly advanced asthma care, particularly therapy, more work is needed to accomplish these goals. In addition, despite the significant proportion of people worldwide who are affected by asthma or other atopic conditions, little effort has been made in assessing and addressing the impact of asthma on the epidemiology of other diseases. Research by our group and others has suggested a potential impact of asthma on susceptibility to other diseases. We postulate that the immunogenetic underpinning of atopic diseases is related to mechanisms underlying an increased risk for other diseases in those with asthma and other atopic diseases.

In this paper, the author makes a case that clinically defined asthma or immunogenetic predisposition to asthma may influence susceptibility to other diseases and suggests that research efforts to identify the etiology of asthma must be juxtaposed to those examining the effects of asthma on various health outcomes. This approach will not only improve asthma care but also enhance efforts to identify the etiology and mechanistic pathways of asthma, because both the etiology and effects of asthma are likely to share the same immunological underpinnings.

The present paper focuses on a primary discussion on the impact of asthma on the risk for microbial infections, using examples of emerging and re-emerging microbial infections, and briefly touches upon the contribution of other atopic conditions to the risk for microbial infections. Subsequently, this discussion is expanded to the risk for chronic pro-inflammatory conditions. Then, the potential mechanisms underlying the association between asthma and other diseases are briefly explored. The final section presents the implications of the scope of this paper related to patient care, research, and public health.

ASTHMA EPIDEMIOLOGY AND THE BURDEN OF THE DISEASE

Asthma is the most common chronic childhood illness and a major cause of morbidity in adults, afflicting 9.6%-13% of children[1,2] and 7.7%-10.1% of adults in the U.S.[2,3] Nearly 30 million Americans and 300 million people worldwide are affected by asthma.[4] A similar asthma incidence has been observed in Olmsted County, Minnesota.[5,6] Based on medical record reviews for 3,059 children, Yawn et al.[6] reported that the prevalence of ever-diagnosed asthma among children in grades K-12 in Rochester (MN, USA) was 17.9% in 1999. There is a debate regarding whether increased asthma prevalence truly exists or is the result of enhanced recognition or changes in diagnostic codes.

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However, given the improved asthma treatment and access to general medical care, the significant increase of asthma mortality over the past three decades in the U.S. suggests a true increase of asthma prevalence.[7-9] At present, there are no overall signs of a declining trend in asthma prevalence; rather, asthma continues to increase in many parts of the world.[10] In addition, other atopic conditions, which share many of the same underlying mechanisms, have prevalence trends similar to that of asthma. For example, studies have reported a significant increase in the prevalence of atopic dermatitis throughout the world.[11,12] In the U.S., the prevalence of atopic dermatitis is 10%-19%,[13-15] affecting 17.8-31.6 million people depending on the criteria for eczema.[13] Allergic rhinitis is also seen in a significant proportion of people in the U.S. (26%-33%; approximately 60 million people).[13-16] Considering the significant proportion of the population affected by asthma and other atopic conditions, determining the impact of asthma on the risk for other diseases at a population level is advisable.

IMPACT OF ASTHMA ON THE RISK FOR RE–EMERGING MICROBIAL INFECTIONS

This section discusses the impact of asthma on the risk for infections caused by *Streptococcus pneumonia* and *Bordetella pertussis (B. pertussis)*, and for mumps, as examples of re-emerging microbial infections.

Asthma and the risk for serious pneumococcal infection

Despite the trend toward reduced risk for invasive pneumococcal diseases (IPD) caused by the heptavalent pneumococcal conjugate vaccine serotypes in the U.S.,[17-19] *Streptococcus pneumoniae (S. pneumoniae)* continues to present a global threat of significant morbidity and mortality among both children and adults. For example, because of emerging serotype replacement,[20] the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention (CDC) now recommends the 13-valent pneumococcal conjugate vaccine for all children. Given the increasing number of pneumococci serotypes, it is difficult to predict whether vaccine manufacturers will continue to keep up with serotype replacement in the future. Neither natural disease nor vaccination provides complete or life-long immunity against reinfection or new disease. Globally, one million children younger than 5 years of age die from pneumonia and IPD each year.[21] In the U.S., the annual number of fatal pneumococcal infections is 40,000.[22] *S. pneumoniae* is responsible for six million cases of otitis media, 100,000 cases of pneumonia, 60,000 cases of sepsis, and 3,300 cases of meningitis per year in the U.S., and nasopharyngeal colonization, a prelude to IPD, occurs in 20%-50% of the population. IPD has a 10% fatality rate for all reported cases (1,556 deaths/15,544 cases). Previous studies have reported that only 50.6% of individuals who developed IPD had at least

one known indication for either the pneumococcal polysaccharide or conjugate vaccine.[23] This indicates that nearly half of IPD cases do not display identifiable risk factors for IPD, suggesting the existence of unidentified risk factors for IPD.

Two recent studies have addressed this question. In 2005, Talbot et al.[24] conducted a case-control study to assess the relationship between asthma and IPD among Medicaid enrollees (children and adults) of the State of Tennessee, using the Active Bacterial Surveillance Program database (1995-2002) of the CDC and the State's administrative Medicaid database. They reported that asthma was significantly associated with the risk for IPD (Odd Ratio [OR], 2.4; 95% Confidence Interval [CI], 1.9-3.2) after adjusting for pertinent covariates and confounders such as high-risk conditions for IPD.[24] The population attributable risk percentage (PAR%) in adults was estimated to be 11%. In an independent population-based case-control study conducted in 2008, our research group found that adults with asthma were at significantly increased risk for serious pneumococcal diseases (SPDs) (IPD and/or pneumococcal pneumonia) compared with adults without asthma (OR, 6.7; 95% CI, 1.6-27.3; P=0.01), after controlling for high-risk conditions for IPD and smoking exposure.[25] The PAR% was 17% in the adult population, whereas the PAR% for all combined ACIP vaccine-eligible conditions in adults was 24%. These data suggest that asthma status alone disproportionately increases the burden of SPD at the population level. As a result of these two studies, the ACIP now recommends a 23-valent pneumococcal polysaccharide vaccine for adults aged 19-64 years who have asthma.

Asthma and the risk for *Bordetella pertussis*

B. pertussis causes whooping cough, a serious respiratory infection affecting 800,000 to 3.3 million people in the U.S. and 50 million worldwide, and causing 300,000 deaths annually.[26-28] *B. pertussis* continues to be a major public health concern, despite the availability of a pertussis vaccine and efforts to improve vaccine uptake. A recent outbreak of nearly 10,000 pertussis cases, as reported to the California Department of Public Health in 2010,[29] highlights the persistence of pertussis as a major threat to public health. During the 1980s and 1990s, pertussis affected primarily infants.[30] During the 2000s, adolescents and adults were disproportionately affected. Among children 10-19 years old, the incidence increased from 5.5 per 100,000 in 2001 to 10.9 per 100,000 in 2003. These data suggest an increase in pertussis incidence due primarily to the waning of humoral immunity over time.

Recently, we reported preliminary results showing an increased risk for pertussis among people with asthma, based on a pertussis outbreak in Olmsted County, Minnesota.[31] The OR for the association between asthma and the risk for pertussis was 1.70 (95% CI, 1.03-2.79; P=0.036); the PAR% of asthma was 15.6%. No population-based study exists for comparison with our preliminary results, but descriptive studies have suggested a po-

tential association between asthma and pertussis.[32,33] The impact of asthma on pertussis epidemiology at the population level is yet to be determined, and it is important to continue to monitor this association.

Asthma and the risk for mumps virus infection

Despite a high vaccine uptake with two doses of mumps vaccine, a large mumps outbreak occurred in the U.S. in 2006.[34,35] A total of 6,584 mumps cases were reported in 2006, but there were no deaths related to the outbreak.[35] This mumps outbreak raises a significant public health concern, as it occurred despite high MMR vaccine coverage. In 2006, the national two-dose coverage among adolescents, who are the highest risk group during a mumps outbreak, was 87%, the highest in U.S. history.[35] Failure of the two-dose vaccine calls for the development of a more effective vaccine or a change in vaccine policy. Nevertheless, neither the public health agencies nor the research community have paid attention to why immunity against the mumps virus diminishes more rapidly than other immunities, and little effort has been made to identify the selective groups at risk for rapid loss of immunity. Previous studies have reported 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.[36] In addition, we recently showed that asthmatic children and adolescents with a family history of asthma had poorer lymphoproliferative responses (a measure of cell-mediated immunity) to mumps and rubella vaccine viruses compared with those without asthma.[37] Previous studies have suggested a temporal waning of anti-rubella antibodies (2.4% decrease per year); thus, without a booster vaccination, individuals may eventually become susceptible to rubella or other viral infections.[38] Our research group recently demonstrated a more rapid decrease of measles virus-specific IgG levels over time in asthmatics compared with non-asthmatics.[39]

Taken together, these studies suggest that asthmatics may lose immunity against mumps or other viruses more rapidly than non-asthmatics and may become a population susceptible to outbreaks of serious infectious diseases. Therefore, a potential epidemiological relationship may exist between asthma prevalence and the 2006 outbreak of mumps in the U.S. This is a research area that deserves further investigation in order to assess whether asthma or other atopic conditions represent an unrecognized selective risk group who require individualized immunization schedules or should be targeted before and during an outbreak, e.g., by sero-surveillance during routine asthma care.

IMPACT OF ASTHMA ON THE RISK FOR EMERGING MICROBIAL INFECTIONS

Asthma may play a role in the risk for new emerging microbial infections such as the 2009 pandemic of novel H1N1 influenza

virus infection. This section illustrates the impact of asthma status on the risk for and severity of novel H1N1 influenza infection by discussing the literature.

On June 11, 2009, the World Health Organization (WHO) declared the first influenza pandemic in 41 years. The WHO reported that as of July 25, 2010, more than 214 countries had been affected by H1N1 influenza, resulting in at least 18,398 deaths worldwide.[40] As of October 2009 (the end of the 2008-2009 influenza season), the CDC reported 50,768 cases of H1N1 influenza in the U.S. Seventy-six (51.7%) deaths were attributed to H1N1 influenza infection.[41]

Although H1N1 influenza infection might not have appeared to be clinically severe, the epidemiological severity of H1N1 influenza was greater than that of seasonal influenza. For example, using "years of life lost" to compare epidemiologic, the 2009 H1N1 pandemic ranks between the 1968 and 1957 seasonal influenza pandemics, and its social impact in terms of missed work days and school days may exceed the social impact of these earlier pandemics.[42]

Our research group carefully examined the studies published during and after the H1N1 influenza pandemic to help assess whether asthmatics displayed an increased risk for and severity of H1N1 influenza infection. During the H1N1 influenza pandemic, two independent studies conducted in the U.S. and Australia-New Zealand showed that the majority of individuals (73%) who developed severe H1N1 influenza (i.e., were admitted to the inpatient floor or intensive care unit) had underlying chronic conditions, with asthma being the most common comorbid condition (28% and 32.7% in the U.S. and Australia-New Zealand studies, respectively).[43,44] In addition, Kloepfer et al.[45] recently reported that compared with non-asthmatics, asthmatics displayed an increased risk for H1N1 influenza infection. Therefore, asthma might have played an important role in the epidemiology of the H1N1 influenza infection.

ATOPIC CONDITIONS OTHER THAN ASTHMA AND THE RISK FOR MICROBIAL INFECTIONS

Atopic conditions other than asthma, including atopic dermatitis and allergic rhinitis, may also affect the risk for microbial infections, as these conditions and asthma share the same underlying immunological mechanisms (i.e., T helper 2 cell-predominant immune profiles).

Atopic dermatitis/allergic rhinitis and the risk for serious pneumococcal disease

After observing the association between asthma and the risk for SPD, we extended our study to assess the role of atopic conditions other than asthma in increasing the risk for SPD.[46] The adjusted odds ratio for the association between atopic conditions other than asthma and SPD was 2.13 (95% CI, 1.04-4.35; P=0.04) after taking into account smoking status, high-risk

conditions for IPD, education status, ethnicity, and asthma status. Thus, like patients with asthma, individuals with other atopic conditions may have increased risk for SPD, independent of asthma status. These results also suggest that the increased risk for SPD in patients with asthma may not be entirely attributable to altered airway architecture; the potentially altered immune functions shared by patients with asthma and those with other atopic conditions may contribute to the increased risk.

Atopic dermatitis/allergic rhinitis and the risk for *Streptococcus pyogenes* infection

We further extended our work to assess the potential association between atopic conditions and other streptococcal infections such as *Streptococcus pyogenes (S. pyogenes)*.[47,48] Patients with asthma showed a higher incidence of *S. pyogenes* infection or colonization (0.25 per person-year; RR, 1.38; 95% CI, 1.12-1.7; *P*=0.003) compared with non-asthmatic patients (0.18 per person-year). Similarly, patients with other atopic conditions (atopic dermatitis and/or allergic rhinitis) displayed a higher incidence of *S. pyogenes* infection (0.24 per person-year; RR, 1.36; 95% CI, 1.12-1.67; *P*=0.004) compared with non-atopic patients (0.17 per person-year) after adjusting for asthma status. These results suggest that patients with either asthma or another atopic condition have increased susceptibility to *S. pyogenes* infections.

Lessons learned from the data

This paper presents several noteworthy findings. First, the increased risk for microbial infections among individuals with atopic conditions other than asthma suggests that the impairment of certain immune functions in asthmatics may play a role in increasing the risk for microbial infection. Recently, our research group showed suboptimal anti-pneumococcal antibody titers in asthmatics compared with non-asthmatics.[49] The literature also shows impaired innate and adaptive immune functions in asthmatics and other atopics (i.e., impaired innate[50-53] and adaptive immunity[54-56]). Second, the data regarding the association between asthma and the risk for microbial infections suggest that an immunogenetic predisposition to asthma poses an increased risk for microbial infections even prior to the development of clinically defined asthma.[47,48] Thus, previous findings on the association between increased bacterial colonization of the airways in infants and subsequent development of asthma at the age of 5 years could be interpreted with reverse causality.[57] In this respect, the relationship between the genetic risk for atopy and a defect in immune cell development leading to immune incompetence may warrant further investigation.[58] Third, the potentially altered immune function in asthmatics and atopics suggests that immune dysregulation may change the risk for non-infectious chronic diseases such as inflammatory bowel syndrome, rheumatoid arthritis, diabetes, and coronary heart disease.

POTENTIAL BIASES AND CONFOUNDERS FOR THE ASSOCIATION

When assessing the association between asthma and the risk for other diseases, systematic biases must be investigated, including detection bias stemming from a situation where the exposure status influences the detection of outcomes and the potential influence of systemic or inhaled corticosteroids on the susceptibility to microbial infection.

Detection bias

The detection of SPD is unlikely to be susceptible to bias, given the serious nature of the disease. However, for other microbial infections, patients with asthma may be more likely to seek medical evaluation for upper respiratory symptoms, and clinicians may be more likely to seek tests or other evaluations in patients with asthma compared with non-asthmatic patients; our research group extensively addressed this concern in previous work.[47,48,59] In a prospective cohort study following 115 children (<4 years of age) for approximately 6 months, we found that the asthma status of the children was not associated with the likelihood of seeking medical evaluation for acute respiratory or gastrointestinal illnesses; the correlation between the frequency of illness and the frequency of seeking care was almost identical between children with and without asthma (ρ: 0.62, *P*<0.001 vs. ρ: 0.64, *P*<0.001, respectively).[59] We recently updated these data by further following the original study cohort, and the proportion of medical evaluations per acute illness among asthmatic and non-asthmatic subjects were 0.41 and 0.39, respectively (*P*=0.75).[60] These results indicate that the parents of asthmatic children are similar to those of non-asthmatic children with regard to the likelihood of seeking medical evaluation for their acutely ill children. We also compared the incidence of *S. pyogenes* infection and the incidence of testing for *S. pyogenes* before and after physician diagnosis of asthma. The incidence of *S. pyogenes* infection did not differ between before and after the diagnosis of asthma (0.28 vs. 0.24 per year, respectively; *P*=0.37), nor did the incidence of testing for *S. pyogenes* infection (0.92 vs. 0.89 per year, respectively; *P*=0.74).[47] Thus, a detection bias is unlikely to entirely explain the relationship between asthma and microbial infections.

Influence of corticosteroid treatment on the risk for microbial infection in asthmatics

Although the literature suggests a potential impact of inhaled corticosteroids on the risk for infection in patients with COPD, this observation has not been well established in patients with asthma.[61,62] In the study results described above, few asthmatic subjects were receiving systemic or inhaled corticosteroids; thus, exposure to corticosteroids is unlikely to account for the findings. In the literature, corticosteroid therapy has not been consistently and significantly shown to be associated with poorer

humoral or cell-mediated responses to vaccines.[63-66] Amid the concern regarding the potential impact of inhaled corticosteroid therapy on the risk for infection, noteworthy findings have been reported. Doull et al.[67] showed no significant benefits from inhaled corticosteroid therapy for viral infection-induced wheezing. In their study, they assessed the percentage of days of upper and lower respiratory tract infection between an inhaled corticosteroid treatment group and placebo group before and after therapy. Although no significant differences between the groups was observed for the frequency of viral infections, post-therapy outcome measures showed a significant reduction in the percentage of days of upper respiratory tract infection (21 to 10 vs. 19 to 16, respectively) and of lower respiratory tract infection (30 to 15 vs. 27 to 21) after inhaled corticosteroid therapy compared with the placebo group. The findings of a potential benefit of inhaled corticosteroids in reducing upper or lower respiratory tract infections did not draw full attention, as the study addressed only the study aims by accepting the null hypothesis (no significant difference) and did not examine either side of the hypothesis testing. Thus, the only conclusions drawn were of no overall increases of infection among subjects treated with inhaled corticosteroids, reassuring patients and clinicians of the safety of inhaled corticosteroids.

Similarly, Martin et al.[68] examined the association between asthma and chronic infections with mycoplasma and Chlamydia. Although a strong association between asthma and infections with mycoplasma and Chlamydia existed, patients on steroid therapy at the time of study enrollment showed a lower frequency of mycoplasma and Chlamydia infections compared to those without steroid therapy. Based on the provided information, an odds ratio for the association between steroid therapy and the risk for mycoplasma or Chlamydia infection was estimated to be 0.34 ($P=0.068$), suggesting a potential protective effect on the risk for such infections.

While corticosteroid therapies, particularly a burst course of systemic steroid therapy and inhaled corticosteroid treatment, do not appear to increase the risk for microbial infections, the literature may not fully address this issue, as the concerns or aims of previous studies have tended to focus on rejecting an alternative hypothesis (accepting the null hypothesis, supporting no difference in the risk for infection between comparison groups). In summary, the association of asthma and other atopic conditions with the risk for microbial infections is unlikely to be fully accounted for by corticosteroid therapies.

IMPACT OF ASTHMA ON THE RISK FOR NON–INFECTIOUS PRO–INFLAMMATORY CHRONIC DISEASES

As discussed above, it is not known whether potential alterations in immune function (i.e., immune dysregulation) in asthmatics and other atopics can result in a predisposition to non-infectious chronic diseases. Sporadic investigations have been conducted using different study designs, various definitions of asthma and other atopic conditions, and different study subjects and settings. To address this question, our research group recently conducted a population-based matched cohort study to assess whether asthma is associated with the risk for developing inflammatory bowel disease, rheumatoid arthritis, diabetes, and coronary heart disease.[69] Asthma was associated with an increased risk for developing diabetes (HR, 2.11; 95% CI, 1.43-3.13; $P<0.001$) and coronary heart disease (HR, 1.47; 95% CI, 1.05-2.06; $P=0.024$), but not with an increased risk for inflammatory bowel disease (HR, 1.31; $P=0.56$) or rheumatoid arthritis (HR, 1.30; $P=0.31$). Previous studies have demonstrated an association between asthma and both coronary heart disease[70] and diabetes.[70-73] The lack of an association between asthma and inflammatory bowel disease and rheumatoid arthritis may be related to systemic corticosteroid therapies in asthmatics. The study was conducted between 1964 and 1983, when systemic steroids were often used for the treatment of asthma, and steroid treatments might have alleviated the progress of inflammatory bowel disease or rheumatoid arthritis. Nevertheless, the data clearly suggest that despite the reciprocal inhibitory relationship between Th1 and Th2 cells at the immunological level, asthma as a Th2-predominant condition does not confer a protective effect on Th1-predominant pro-inflammatory conditions, but may increase the risk for other conditions.

POTENTIAL MECHANISMS UNDERLYING THE ASSOCIATION BETWEEN ASTHMA AND OTHER DISEASES

Conceptualizing the mechanisms underlying the association of asthma with microbial infections and non-infectious pro-inflammatory chronic conditions is not a simple task, given the multiple requirements accounting for the association. If asthma were to causally affect the risk for other diseases, it appears clear that alterations in airway architecture and the previously reported impairments of innate immunity in asthmatics would unlikely be sufficient to account for the associations, given that adaptive immune functions are probably involved with the processes discussed above (e.g., the waning of immunity, suboptimal cell-mediated immunity, and involvement with other inflammatory diseases). Indeed, the literature provides some sporadic support for altered or impaired adaptive immune functions in asthmatics and other atopics.[54-56] The mechanisms underlying the association between asthma and other diseases are likely to be related to the immunogenetic underpinnings of atopy. A Th2-predominant immune environment has been shown to be associated with susceptibility to and severity of a broad range of microbial infections, including Gram-negative bacteria,[74,75] virus,[76-79] protozoa,[80-82] mycoplasma,[83] and candidiasis,[84] in animal models. However, the ways in which the Th2-predominant immune milieu or cytokines affect the risk for mi-

crobial infection, as well as for other inflammatory conditions, has not yet been determined. Many active research studies are investigating the mechanisms of the increased risk for infection in asthmatics and other atopics.

Our research group has assessed the potential role of human leukocyte antigen (HLA)-DR polymorphisms in the associations described above. We previously reported an association between the HLA-DR3 gene and childhood asthma,[85] and demonstrated that this association was independent of linkage disequilibrium with the ancestral haplotype 8.1.[86] Importantly, using a humanized transgenic mouse model with no mouse MHC genes and carrying the HLA-DR3 or HLA-DR2 gene, we showed significant Th-2 predominant airway inflammation and immune responses after sensitization and challenge with house dust mite (a significant increase of eosinophils and IL-4 in BAL) in DR3-carrying mice compared with DR2-carrying mice (the DR2 gene was not associated with asthma, according to our epidemiologic study).[87] These data suggest a potential HLA-DR restriction for recognizing house dust mite. In support of this finding, the HLA-DR3 gene has been reported to be associated with atopic asthma or allergic sensitization, including to house dust mite.[88-90] Other studies have suggested a HLA-D gene restriction for recognizing house dust mite.[91] Furthermore, a recent genome-wide association study has identified the HLA-DR gene as a susceptibility gene for asthma.[92]

According to the literature, the HLA-DR3 gene is associated with suboptimal immune responses. Previous studies have reported that HLA-DRB1*03 is associated with poor immune responses to various vaccines (measles,[93] hepatitis B,[94] and tetanus toxoid[95]) and a nasopharyngeal carrier status of *Staphylococcus aureus*.[96] In addition, the HLA-DR3 gene has been shown to be associated with a risk for autoimmune disease.[97,98] Although these authors did not suggest a mechanism for the association between asthma and the risk for other diseases, a biologically plausible mechanism may be explored. Different approaches may be used for identifying the mechanism of asthma etiology versus determining the effects of asthma, but the results of the two lines of study are likely to advance both goals. Thus, research toward both goals should be performed in parallel.

THE IMPLICATIONS

Patient care

At present, current asthma care focuses on the control of asthma primarily through pharmacological therapies, environmental control, and patient education. However, new approaches for patient care can be considered. First, the early identification and appropriate treatment of microbial infections or other chronic diseases associated with asthma may be worthwhile. For example, the ACIP recommendation that asthmatics aged 19-64 years old should receive 23-valent pneumococcal polysaccharide vaccinations could be implemented. In addition,

other possible causes for conditions associated with asthma should be evaluated. A lingering coughing episode may not be the result of uncontrolled asthma, but rather the result of pertussis, given the increased risk for pertussis in asthmatics. A chest pain may not be due to asthma, but may be an early manifestation of coronary heart disease, given the potential association between asthma and coronary heart disease, although the counteracting treatment approaches for asthma and coronary heart disease may be challenging. In this respect, specific recommendations for how to assess and address the conditions associated with asthma could be included in asthma guidelines. Second, along these lines, asthmatics may require individualized immunization schedules and a specific monitoring plan. In the U.S., decennial Td (tetanus and diphtheria) vaccines after Tdap at ages 11-12 years may need to be replaced with Tdap for asthmatics, given the significant increase of pertussis among asthmatics and the major cyclic pertussis outbreaks. Assessment of vaccine durability (e.g., pertussis immunity or MMR immunity) during a routine follow-up visit for asthma care could be considered, and asthmatics exhibiting decreased immunity could receive a booster dose of vaccine. However, careful cost-benefit and patient safety analyses must be performed before implementation of this approach. Finally, when new approaches are phased into patient care, their effectiveness needs to be studied through integration of both research and clinical practice.

Public health

First, when an outbreak of emerging or re-emerging infectious disease occurs, epidemiological investigations by public health agencies must assess the role of asthma or other atopic conditions in the risk for or severity of infection. It would also be important to monitor the impact of asthma epidemiology on the epidemiology of emerging and re-emerging infectious diseases and of other chronic diseases. To date, little effort has been made to address the question of why some people acquire an infection and others do not. The role of asthma in the 2009 H1N1 influenza outbreak may represent a prime example, as discussed above. Second, the increased risk for microbial infections in asthmatics could be a biodefense or bioterrorism issue, as asthmatics in the general population and in the military may be disproportionately affected by exposure to a biological assault. Finally, it would be worthwhile for public health agencies to perform a well-designed surveillance for the influence of asthma on the epidemiology of other chronic diseases, including inflammatory diseases and malignancy as described above.

Research

Systematic research to clarify the association of asthma, as well as atopic conditions other than asthma, with microbial infections, particularly vaccine-preventable infections, and chronic diseases should be undertaken. Research should also address

the question as to why some asthmatics have increased risk for infection and disease, while other asthmatics do not. Asthmatics with increased susceptibility to microbial infections and other diseases may represent a different asthma phenotype, perhaps with different etiologic processes. This is largely overlooked in the current literature and warrants further study. Airway colonization by bacteria or other organisms may provide an important surrogate marker for identifying asthmatics with a susceptibility phenotype. Our research group and others are actively pursuing research in this area. Finally, the identification of a mechanism that accounts for the etiology and effects of asthma under a "unified theory" presents a formidable task. Collaborative research efforts coordinated among multidisciplinary research groups can increase the opportunities for pertinent discoveries leading to such a theory.

ACKNOWLEDGMENTS

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