

The health threats to people with asthma through asthma-associated infectious disease comorbidities are largely under-recognized

In this issue of *Journal of Internal Medicine*, Helby *et al.* reported that compared to individuals without asthma or other atopic conditions, nonsmokers with early asthma (<50 years of age) defined by self-report had increased risk of any infections (hazard ratio (HR) of 1.65, 95%CI: 1.40–1.94), pneumonia (HR of 2.44, 95%CI: 1.92–3.11), and nonrespiratory tract infections (HR: 1.36, 95%CI: 1.11–1.67) defined by ICD codes in their large-scale prospective cohort study which followed 105 519 individuals from the general population of the City of Copenhagen, Denmark, for a median duration of 6 years [1]. These findings were fairly consistent across subgroups of asthma stratified by various clinical characteristics of asthma including a smoking history, a history of hospitalization, lung function, asthma medications, duration of asthma and presence of other atopic conditions. Also, using outcomes less susceptible to a detection bias such as mortality, they also found that ever smokers with asthma had significantly higher mortality from any infections (HR: 1.77, 95%CI: 1.47–2.13), pneumonia (HR: 1.87, 95%CI: 1.51–2.31) and nonrespiratory infections (HR: 1.62, 95%CI: 1.18–2.23), compared to those without asthma or other atopic conditions.

There are a few important aspects of this study worth discussing. *First*, to date, this is the largest prospective cohort study amongst the existing clinical studies which have addressed the relationship between asthma and the risk of infections [2–4]. Given the large-scale of this prospective cohort study, the rationale to define asthma status and infectious outcomes by self-report and ICD codes, respectively, is understandable. Overall, the study was well designed in terms of minimizing susceptibility bias (e.g. by stratifying smoking status and age of asthma onset) and detection bias (e.g. limiting to clinically more significant infectious diseases and death, and validation of ICD codes for infection). One limitation in their study was that the role of individual asthma medications such as

inhaled corticosteroids (ICS) was not assessed in the context of susceptibility bias, although there is little evidence supporting increased risk of infections such as pneumonia amongst patients with asthma by ICS [5]. Whilst there are previous studies supporting the association between asthma and the risk of pneumococcal diseases [2–4], they tend to be based on specific local populations and a study based on the general population is, indeed, limited as claimed by Helby *et al.* In support of this presented work, a recent retrospective study based on the claim data of the general population of Korea showed a threefold increase of invasive pneumococcal disease amongst adults and children with asthma [6].

Secondly, the study reported a novel finding on the association of asthma with the risk of nonrespiratory infections. Early asthma amongst all individuals (without regard to smoking history) had increased risk of nonrespiratory infections including skin infection, urinary tract infection, sepsis and diarrhoeal disease (Figure S3). Previous studies concerning the association of asthma with the risk of infections have focused on pneumococcal diseases because the original epidemiological concern was a smaller number of patients with pneumococcal vaccine-eligible conditions amongst those who developed invasive pneumococcal diseases than expected, only 50.6% [7, 8]. There are only a handful of previous studies on the association of asthma with nonpneumococcal infections including nonrespiratory infections. This is one reason why health threats to people with asthma through asthma-associated infectious disease comorbidities are under-recognized by patients, their caregivers, clinicians and researchers apart from the fact that the literature concerning heterogeneity of asthma does not consider the risk of infections amongst people with asthma as a distinctive phenotype. In this respect, the work of Helby *et al.* adds important evidence supporting that the impact of asthma on susceptibility to

infections goes beyond the airways, but they did not examine the specific organisms underlying both pneumonia and nonrespiratory infections. Overall, the study results are consistent with the current literature suggesting the association of asthma with the risk of a broad range of infections. For example, our group has reported the increased risk of pertussis [9], breakthrough varicella infection [10], *Streptococcus pyogenes* infection [11], herpes zoster [12, 13], community-acquired *E. coli* blood stream infection [14] and appendicitis [15], and these results were supported by the work of others [16–19]. Again, these study results suggest that asthma poses increased risk of a broad range of infections from respiratory, urinary and gastrointestinal infections. Furthermore, our prior work demonstrated that asthma poses increased risk of inflammatory diseases including the risk of incident myocardial infarction, diabetes mellitus (DM) and rheumatoid arthritis [20–22]. Interestingly, examining the characteristics of study subjects reported by Helby *et al.* (Table 1), late asthma (>50 years) disproportionately represented patients with diabetes mellitus (DM) (6.7%), compared to healthy individuals (3.9%). Perhaps, Helby *et al.* may consider analyzing the relationship between asthma and the risk of inflammatory diseases in follow-up to their present study.

Thirdly, the authors reported population attributable fractions (PAF) for any infection amongst never smokers with asthma ever (2.2%), compared to that for those with DM (2.9%) suggesting similar PAF for asthma and DM. This is thoughtful analysis, and the results provide an insight into grasping the nature and magnitude of the impact of asthma on the risk of infections in relation to a chronic disease with its known effect on susceptibility to infections such as DM. They did not report PAF for pneumonia amongst subjects with asthma versus DM, but PAF for pneumonia amongst subjects with asthma seems to be significantly greater than those with DM. Klemets *et al.* reported ~5% of invasive pneumococcal infections were attributable to asthma [23]. At any rate, this result highlights the under-recognized impact of asthma on risk of infections despite its major threats to health of people with asthma and poses major significance in public health and clinical practice.

Finally, the mechanisms underlying the association between asthma and the risk of infections are largely unknown, but the impairments in both innate and adaptive immunity are important

factors as described in the recent review and commentaries [2–4]. As these previous studies tend to report the primary immune dysfunction or epithelial barrier defect, few studies examined the possibility of waning of immune functions over time (e.g. the secondary vaccine failure for vaccine-induced immunity). We recently reported that measles vaccine virus-induced humoral immunity wanes more rapidly amongst children with asthma, compared to those without asthma (a decrease of -0.114 unit per year versus a decrease of -0.046 unit per year, respectively, $P = 0.010$) [24]. Importantly, this waning of vaccine-induced immunity affected seropositivity (73% vs. 84%, $P = 0.038$) might take place even before the development of clinical asthma. The rapid waning of vaccine-induced adaptive immunity may account for, in part, the reasons why people with asthma had increased risk of vaccine-preventable diseases such as breakthrough varicella [10] and pertussis [9]. The finding on a more rapid waning of immunity prior to the onset of clinical asthma is also reminiscent of the study findings reported by Bisgaard *et al.* which suggest that children who subsequently developed asthma already had abnormal lung function at the time of birth [25] and increased risk of colonization by pathological bacteria during infancy [26], compared to those without asthma. Collectively, these data may suggest that the mechanisms underlying the increased risk of infections associated with asthma may encompass immunogenetics and take place early in life.

Some evaluative and therapeutic approaches for asthma-associated infectious disease comorbidities can be considered whilst the underlying mechanisms are explored. *First*, being aware of the increased risks of infections amongst people with asthma is important. For example, when asthma patients have chronic uncontrolled cough, they should not assume it is due to asthma but be checked for possible infections (e.g. pertussis [9], mycoplasma or chlamydia [2, 27, 28]). If positive for vaccine-preventable infections such as pertussis, serologic titres can be checked for a possibility of waned immunity for Tdap in children and adolescents including diphtheria and tetanus and re-immunize them if waned. *Secondly*, as the risk of certain infections depends on asthma severity or control status [29], patients and clinicians should make every effort to control asthma and reduce the risk of asthma exacerbations using preventive and therapeutic interventions. In this respect, as ICS

plays an integral part to control asthma and reduce the risk of asthma exacerbations, with little to do with the risk of infections or even potentially reduces risk of less serious pneumonia [5], patients and clinicians should not be hesitant to use ICS for asthma. *Thirdly*, all individuals with asthma should be vaccinated according to the age-appropriate schedule without concerns about proper primary immune responses. In this respect, there may be a need for an individualized vaccine schedule (or even dosing) for people with asthma, at least a subgroup of asthmatic individuals who are prone to lose immunity [24]. Clinicians and patients with asthma need to be reminded that the ACIP, a vaccine policy governing body in the United States, now recommends a single dose of PPV-23 to adults with asthma aged 19–64 years. In addition, a few additional vaccines can be individualized for people with asthma. For example, given the high prevalence of asthma and the ongoing risk of pertussis throughout the United States, consideration of defining people with asthma as a target group for pertussis vaccination (e.g. replacing decennial Td booster with Tdap vaccine) should be given [9]. With the same reasons, consideration for immunizing adults with asthma or atopic dermatitis over 50 years or older as a target group for zoster vaccine should be given [13] as the current adult zoster vaccine is approved for 50 years or older by FDA until a new zoster vaccine is available [30, 31]. Along these lines, people with asthma who develop vaccine-preventable diseases as described above may need to be checked for immune titres for other vaccine-preventable diseases and be revaccinated if waned. *Fourthly*, in my opinion, if proper initial evaluations for the known risk factors for asthma-associated infections (e.g. primary immunodeficiency) do not reveal any known causes, routine, further, and costly testing (e.g. searching genomic variants with uncertainty of clinical significance) to identify causes may be unnecessary in asthmatic patients until we know more about the mechanisms and clinical features. Finally, it is time for professional organizations concerning asthma care and research to address asthma-associated infectious disease comorbidities in their guidelines. When a new challenge emerges (whatever it is) at the time when responses are seemingly premature, the first step is to recognize it in a timely manner.

In conclusion, the study by Helby *et al.* adds important evidence supporting the impact of asthma on the risk of a broad range of respiratory and nonrespiratory infections. We commend the

investigative team and the study participants for making this important study feasible. It is an urgent need to have strategies for how to identify a subgroup of people with asthma at risk of asthma-associated infectious disease comorbidities and effectively manage them to mitigate the risk and outcomes of such conditions as currently, no guidelines for identification and management of such conditions exist.

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Conflict of interest statement

No conflicts of interest to declare.

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