Increased risk of cutaneous and systemic infections in atopic dermatitis – A cohort study

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Short title: Infections in atopic dermatitis

Abbreviations:

Atopic dermatitis	AD
Serious pneumococcal disease	SPD
The Health Improvement Network	THIN
General Practice	GP
United Kingdom	UK
Analysis of variance	ANOVA
Confidence interval	CI

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To the Editor

Atopic dermatitis (AD, also known as atopic eczema or eczema), is characterized by skin barrier and immunologic dysfunction. Viral and bacterial super-infection of cutaneous lesions including eczema herpeticum and staphylococcus aureus in patients with severe disease is well documented (Ong and Leung, 2016, Weidinger and Novak, 2016). Whether the general population of patients with AD has an increased risk of these and other types of infections due to an impaired skin barrier and/or immunologic dysfunction is unclear.

A recent meta-analysis of genome wide association studies identified mutations in genes thought to play roles in the regulation of innate and adaptive immunity, in addition to established barrier function susceptibility loci such as filaggrin (Paternoster et al., 2015). Investigations of skin physiology suggest that differences in barrier function are identifiable very early in infancy and are highly predictive of the development of AD (Kelleher et al., 2015). We therefore hypothesized that individuals who develop AD are at increased risk of infections due to underlying genetically influenced immune and barrier dysfunction. The objective our study was to determine if there was an association between AD and multiple common cutaneous and non-cutaneous infections.

We performed a cohort study using The Health Improvement Network (THIN), a medical records database that is representative of the UK general population (Seminara et al., 2010). Ethics approval for this study was obtained from the THIN Scientific Review Committee and the University of Pennsylvania IRB. We included 3,112,617 individuals registered prior to age 18 who were followed for a mean of 13.7 years (Standard deviation 13.6, 13.7). We identified subjects with AD based on the presence of at least one of any of the following diagnostic codes on two different visits, as is common practice in studies of chronic conditions using electronic health data (Herrett et al., 2010): Atopic dermatitis and related conditions (M11.00) Atopic dermatitis/AD (M111.00), Atopic dermatitis NOS (M11z.00). The prevalence of AD was 14.4% (95% CI:14.4,14.4).

We examined the prevalence of multiple common cutaneous and non-cutaneous infections (warts, dermatophyte infection, impetigo, molluscum contagiosum, otitis media, pneumonia, and streptococcal throat infection; codes available in Supplemental Table 1). We found that all of the infectious illnesses we had determined to test *a priori* were more prevalent in those with AD. Using multilevel mixed effects logistic regression, we examined the odds of each infectious outcome at any time point, and found that the strength of association for cutaneous infections varied from a 55% increased odds of impetigo to a three-fold increased odds of molluscum contagiosum after adjusting for gender, age, time of observation and practice. Associations with non-cutaneous infections varied from 27% increased odds of streptococcal throat infections to a two-fold increase in otitis media (Table 1).

We performed sensitivity analyses exploring the definition of AD. When we estimated the association with a longer list of less specific ‘dermatitis’ codes (Supplemental Table 1), we found the majority of the associations were diminished. When we estimated the association with a more narrow designation ‘AD plus asthma or seasonal rhinitis’, the magnitude of most of the

associations increased. This highlighted a potential link between underlying immune dysfunction in atopic disease and increased susceptibility to infection.

Prior publications have found higher rates of infections among patients with AD, but most are from clinical populations that are likely to represent the more severe end of the AD spectrum (Beck et al., 2009; Peng et al., 2007), or are based on patient self-report and may be subject to recall and misclassification biases (Silverberg and Silverberg, 2014, Strom and Silverberg, 2016). Indirect evidence also comes from multiple studies that show an association between antibiotic use in early life and AD (Schmitt and Weidinger, 2014; Tsakok et al., 2013).

Strengths of this study include physician-confirmed diagnoses and a large longitudinal population-based sample. A number of potential limitations also warrant discussion. Our finding of an increased risk of cutaneous infections could be due to ascertainment bias (i.e. individuals with AD are more likely to have their skin checked and have skin conditions diagnosed). Though it is less likely that AD patients would have differential recording of systemic infections such as otitis or pneumonia, there may be a lower threshold for diagnosis or treatment of upper respiratory infections among patients with comorbid asthma, given the concern for asthma exacerbations with viral illness. Moreover, patients with chronic conditions like AD may be more likely to seek care. Nonetheless, our findings are important from a resource planning perspective; additional research is needed to understand the causal relationship between AD and infections. Finally, because AD can have a heterogeneous presentation, diagnosis may occasionally require specialist care, and we did not have access to dermatologist records. However we believe our reliance on general practice physician records is reasonable in this context given that the vast majority (97%) of AD in the UK is treated in primary care (Emerson et al., 1998; Schofield JK, 2009).

We did not have detailed data about disease severity, flares, or timing of treatment use. Future studies examining whether there is a temporal association between these factors and infections could provide clinically useful prognostic information. Additionally, information on the timing of treatment use relative to infections could help to establish whether specific treatment improves barrier function and reduces infection risk, or whether immunosuppressive treatment increases infection risk. Because we studied the risk of infection at any time point (including prior to AD diagnosis and treatment), our results are unlikely to be confounded by immunosuppressive treatment use for AD. As noted above, multiple studies have demonstrated an association between AD and early life antibiotic exposure, which provides support for our hypothesis that patients with AD are at an increased risk of infection even prior to AD diagnosis, and/or could indicate an effect of antibiotics on the development of AD (Schmitt and Weidinger, 2014; Tsakoket al., 2013). Additional work is needed to determine whether antibiotic treatment plays a causal role in the development of AD.

In summary, we found increased risks of all infectious outcomes examined, which include both cutaneous and non-cutaneous infections caused by bacteria, viruses, and fungi. This observation raises numerous questions about the nature of immunological defects in AD. One study found that subjects with AD in whom eczema herpeticum develops have more severe Th2-polarized disease, more atopic comorbidities, and more cutaneous infections (Becket al., 2009). Our study adds epidemiologic evidence suggesting that AD patients may additionally be at risk of non-

cutaneous infections. A significant body of functional and genotype/phenotype data has been developed for filaggrin (McAleer and Irvine, 2013); and there is a need for similar work linking immunological defects to clinical phenotypes.

Determining if individuals with AD are at increased risk of infections is important to guide the development of screening and prevention programs to reduce the morbidity associated with AD. Moreover, a baseline understanding of infectious risk is particularly important in the context of introduction of the many new biologic therapies now in the pipeline for AD.

Table 1. Prevalence and risk of infectious outcomes among those with AD as compared to those without AD

	Descriptive statistics		***Primary Analysis*** Risk of infectious outcome ever		***Sensitivity Analysis*** Risk of infectious outcome ever using different exposure definitions	
Variable	**Overall prevalence (N=3,112,617)**	**Prevalence among those with AD (N =448,311)**	**Crude**	**Adjusted***	**Dermatitis (N =632,707) Crude**	**AD and asthma and/or rhinitis (N=162,116) Crude**
	N % (95% CI)	**N % (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Cutaneous Infections						
Cutaneous warts	285,011 9.12 (9.12,9.19)	72,681 16.21 (16.10,16.32)	2.23 (2.21,2.25)	1.98 (1.96,2.00)	1.50 (1.48,1.53)	2.91 (2.87,2.95)
Dermatophyte infection	24,693 0.79 (0.78, 0.80)	7,899 1.76 (1.72,1.80)	2.83 (2.75,2.90)	2.54 (2.47,2.61)	2.14 (2.02,2.26)	3.56 (3.44,3.69)
Herpes simplex virus	65,027 2.09 (1.07,2.10)	18,461 4.11 (4.06,4.18)	2.41 (2.37,2.46)	2.08 (2.04,2.12)	1.81 (1.75,1.88)	3.26 (3.19,3.34)
Impetigo	21,467 0.69 (0.68,0.70)	7,899 1.76 (1.72,1.80)	3.50 (3.41,3.60)	1.55 (1.47,1.64)	2.06 (1.96,2.18)	3.82 (3.69,3.96)
Molluscum contagiosum	118,325 3.80 (3.78,3.82)	43,997 9.81 (9.73,9.90)	3.79 (3.74,3.84)	3.11 (3.07,3.14)	1.82 (1.78,1.86)	3.50 (3.44,3.56)
Systemic Infections						
Otitis media	744,512 23.92 (23.87,23.97)	192,112 42.85 (42.71,43.00)	2.87 (2.85,2.88)	2.24 (2.22,2.25)	1.74 (1.72,1.76)	3.43 (3.40,3.47)
Pneumonia	69,880 2.24 (2.22,2.26)	17,087 3.81 (3.76,3.87)	1.96 (1.93,1.99)	1.27 (1.23,1.31)	1.48 (1.44,1.53)	2.76 (2.69,2.82)
Streptococcal throat infection	18,271 0.59 (0.58,0.59)	4,558 1.02 (0.99,1.05)	1.98 (1.92,2.05)	1.34 (1.26,1.42)	1.38 (1.30,1.46)	2.72 (2.60,2.84)

Notes: *Adjusted for age at registration, gender, and time under observation. Physician practice included as a random effect in the model.

Conflict of interest

Dr Margolis is on separate data safety monitoring boards for Astellas, Janssen, Regeneron/Sanofi, and GlaxoSmithKline; the remaining authors state no conflicts of interest.

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