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Increased Risk of Cutaneous and Systemic Infections in Atopic Dermatitis—A Cohort Study



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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 superinfection 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 because of 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 because of underlying genetically influenced immune and barrier dysfunction. The objective of our study was to determine if there was an association between AD and multiple common cutaneous and noncutaneous infections.

We performed a cohort study using The Health Improvement Network, 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 Health Improvement Network Scientific Review Committee and the University of Pennsylvania Institutional Review Board. We included 3,112,617 individuals registered before age 18 years who were followed for a mean of 13.7 years (95%

confidence interval = 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), and atopic dermatitis not otherwise specified (M11z.00). The prevalence of AD was 14.4% (95% confidence interval = 14.4–14.4).

We examined the prevalence of multiple common cutaneous and noncutaneous infections (warts, dermatophyte infection, impetigo, molluscum contagiosum, otitis media, pneumonia, and streptococcal throat infection; codes available in [Supplementary Table S1](#) online). 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 3-fold increased odds of

Abbreviation: AD, atopic dermatitis

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

Variable	Descriptive Statistics		Primary Analysis: Risk of Infectious Outcome Ever		Sensitivity Analysis: Risk of Infectious Outcome Ever Using Different Exposure Definitions	
	Overall Prevalence (n = 3,112,617)	Prevalence among Those with AD (n = 448,311)	Crude	Adjusted ¹	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)

Abbreviations: CI, confidence interval; OR, odds ratio.

¹Adjusted for age at registration, sex, and time under observation. Physician practice included as a random effect in the model.

molluscum contagiosum after adjusting for sex, age, time of observation, and practice. Associations with non-cutaneous infections varied from 27% increased odds of streptococcal throat infections to a 2-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 (see Supplementary Table S1), we found that most 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, and therefore 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 therefore 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). Although 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, 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 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 before AD diagnosis and treatment), our results are unlikely to be confounded by immunosuppressive treatment use for AD. As noted, multiple studies have shown 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 before AD diagnosis, and/or could indicate an effect of antibiotics on the development of AD (Schmitt and Weidinger, 2014; Tsakok et 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 noncutaneous 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 T helper type 2 cell-polarized disease, more atopic comorbidities, and more cutaneous infections (Beck et 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 the introduction of the many new biologic therapies now in the pipeline for AD.

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CONFLICT OF INTEREST

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

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at <http://dx.doi.org/10.1016/j.jid.2017.01.030>.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1. Codes for exposure and outcomes

AD	Dermatitis	Cutaneous warts	Streptococcal throat infections	Pneumonia	Impetigo	Herpes simplex virus	Molluscum contagiosum	Allergic rhinitis	Otitis media	Asthma	Dermatophyte infections
M114.00	Myu2.00	7G09111	A340.00	4JUK.00	M05z.00	Q402000	43jb.00	14B1.00	F501G00	12D2.00	AB04.00
M113.00	Myu2200	A781400	A34..00	A022200		A54y.00	A780.00	1C83.13	F512100	14B4.00	AB04.12
M112.00	M114.00	A781.11	A340z00	A116.00		A544500	A780000	H00..16	F501C00	173A.00	
M111.00	M11..00	A781.00	A34z.00	A380300		A531z00		H120.00	F514000	173c.00	
M12z100	M11z.00	A781600	A340300	A3B2.00		9kF8.00		H120000	F501D00	178..00	
	M111.00	7G09011	A3B0.00	A3BXA00		A53y.00		H120100	F501411	1781	
	M119.00	A781000	A340100	A3BxB00		A54x.00		H120200	F502300	1782	
	M12z111	ZA3..00	A340200	A3C0300		A531000		H120300	F513111	1783	
	A540.00	8BAZ.11		A54x400		A532000		H120z00	F514300	1784	
	M12z100	7G06111		A551.00		A544100		H17..00	F502500	1785	
	F502411			A730.00		A53x.00		H17..11	F510300	1786	
	F4D3000			AB24.11		A53xz00		H170.00	F501B00	1787	
	M12z400			H06z100		A532z00		H170.11	F513000	1788	
	12H1.00			H06z112		A532100		H171.00	F513100	1789	
	M113.00			H2...00		A544z00		H171.14	F501y00	178A.00	
	14F1.00			H20..00		F030411		H172.00	F512z00	178B.00	
	M12z300			H20..11		A544000		H172.11	F522.00	1J70.00	
	M112.00			H200.00		A541400		H17z.00	F501E00	1O2..00	
	M12z200			H201.00		A531100		H330.13	F511100	2126200	
	M102.00			H202.00		A54x300		H330011	F502600	212G.00	
	M07y.11			H20y.00		A546.00		Hyu2000	F513z00	38DL.00	
	M102.11			H20z.00		65PQ.00			F510200	663..11	
	M101.12			H21..00		A541z00			F511300	663e.00	
				H21..11		9kF8.11			F513.00	663f.00	
				H22..00		A53x000			F514.00	663N100	
				H22..11		A544300			F524000	663N200	
				H220.00		A532300			F501z00	663O.00	
				H221.00		A541500			F511200	663O000	

H222.00	A548.00	F520100	663p.00
H222.11	A541000	F511.11	663P.00
H223.00	A54z.00	F521.00	663r.00
H223000	A544.00	F524.00	663t.00
H224.00	2524.00	F511z00	663v.00
H22y.00	A544200	F520000	663V100
H22y000	A54..11	F518.00	663V300
H22y011	2524.12	F502400	663w.00
H22y200	A54z.11	F520z00	663W.00
H22yX00	A541.00	F514z00	663x.00
H22yz00	A54..00	F512000	66Y5.00
H22z.00	A542.11	F510000	663h.00
H23..00		F512.00	663j.00
H23..11		F510z00	663m.00
H231.00		F525.00	663n.00
H232.00		F514100	663N.00
H233.00		F510011	663N000
H23z.00		F502700	663Q.00
H24..00		F511.00	663s.00
H240.00		F501100	663U.00
H241.00		F510100	663u.00
H242.00		F501F00	663V.00
H243.00		F514200	663V000
H243.11		F523.00	663V200
H246.00		F501000	663y.00
H247000		F512.12	66Y9.00
H247z00		F528.00	66YA.00
H24y.00		F520.00	66YC.00
H24y000		F512.11	66YE.00
H24y200		F52z.11	66YJ.00
H24y300		F526.00	66YK.00
H24y400		F527.00	66YP.00

H24y600	F502.00	66Yp.00
H24y700	F52..00	66YQ.00
H24yz00	F510.00	66Yq.00
H24z.00	F502z00	66Yr.00
H25..00	F501.00	679J.00
H25..11	F52z.00	66YR.00
H26..00	F510500	66Ys.00
H260.00		68C3.00
H261.00		8CMA000
H262.00		8CR0.00
H270.00		8H2P.00
H270.11		8791
H270000		8793
H270100		8794
H270z00		8795
H28..00		8796
H2B..00		8797
H2C..00		8798
H2y..00		8HTT.00
H2z..00		9N1d.00
H470.11		9NNX.00
H470312		9OJ..00
H471000		9OJ..11
H530300		9OJ1.00
H540000		9OJ2.00
H540100		9OJ3.00
H564.00		9OJ4.00
H564.11		9OJ5.00
H56y000		9OJ6.00
H56y100		9OJ7.00
H571.00		9OJ8.00
Hyu0800		9OJ9.00

	Hyu0A00	9QJA.00
	Hyu0B00	9QJA.11
	Hyu0D00	9QJZ.00
	SP13100	9Q21.00