Published in final edited form as:

Ann Allergy Asthma Immunol. 2018 January ; 120(1): 66–72.e11. doi:10.1016/j.anai.2017.10.019.

Association between atopic dermatitis and serious cutaneous, multiorgan and systemic infections in US adults

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Keywords

atopic dermatitis (AD); burden; cost of care; eczema; hospitalization; inpatient; length of stay; morbidity; mortality; prognosis; serious infection; skin infection; systemic infections

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting 13% of children¹ and 7–10% of adults^{2, 3} across the United States. It is well established that AD is associated with a higher incidence of certain cutaneous infections, including *Staphylococcus aureus* colonization, molluscum contagiosum and eczema herpeticum (EH)^{4–6}, and possibly

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JI Silverberg had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: JI Silverberg

Acquisition of Data: JI Silverberg, S Narla

Analysis and interpretation of data: S Narla, JI Silverberg, Drafting of the manuscript: S Narla, JI Silverberg

Critical revision of the manuscript for important intellectual content: S Narla, JI Silverberg

Statistical analysis: JI Silverberg, S Narla

Obtained funding: JI Silverberg

Administrative technical or material support: None

Study supervision: None

Financial disclosures: None

Foundation and American Medical Association Foundation.

Design and conduct of the study? No

Collection, management, analysis and interpretation of data? No

Preparation, review, or approval of the manuscript? No

Decision to submit the manuscript for publication? No

Conflicts of interest: None

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cutaneous warts⁷. In fact, predisposition toward cutaneous infection is one of the Hanifin and Rajka minor diagnostic criterion for AD⁸. The mechanism of such predisposition is thought to be multifactorial, including impaired epidermal barrier function⁹, decreased expression of antimicrobial peptides¹⁰, and abnormal innate immune response in skin¹¹.

Recent US population-based studies showed that AD is also associated with higher rates of extra-cutaneous infection in both children^{7, 12} and adults¹³, such as infections of the upper and lower respiratory tracts, ears and urinary tract. Those studies utilized surveys with questions about self- or caregiver-reported AD and infections. In the present study, we sought to determine whether there is an association between healthcare diagnosed AD and serious infections in adults. We hypothesized that adults with AD have significantly higher prevalences of cutaneous, respiratory, multi-organ and systemic infections.

Methods

Data Source

The 2002–2012 Nationwide Inpatient Sample (NIS) provided by the Healthcare Cost and Utilization Project (HCUP) from the Agency for Healthcare Research and Quality (AHRQ) was analyzed. Each year of NIS contains an approximately 20% stratified representative cross-sectional sample of all US hospitalizations. Sample weights were created by NIS that factored the sampling design of hospitals in the US. These sample weights allow for representative estimates of hospital discharges across the whole country. All data were de-identified and no attempts were made to identify any of the individuals in the database. All parties with access to NIS were compliant to HCUP's formal data use agreement. The study was approved by the institutional review board at Northwestern University.

Identification of AD and serious infections

The databases were searched for a primary and/or secondary diagnosis of AD or eczema using the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes 691.8 and 692.9. A previous study validated the use of the discharge diagnosis code 691.8 in the inpatient setting for the study of AD¹⁴. We also found that the ICD-9-CM codes for AD (691.8) and eczema (692.9) are used interchangeably in the outpatient setting, with a large number of AD patients being coded as eczema¹⁴. Thus, the primary analyses were done for AD and eczema (AD-E) combined. In addition, sensitivity analyses were performed that examined AD alone. This approach provided a range of cost and LOS estimates, recognizing that analysis of AD alone underestimates the true prevalence and AD-E may overestimate the true prevalence.

The control group included all hospitalizations without any diagnosis of AD-E, yielding a representative cohort of US hospitalizations. Previous studies showed higher rates of serious infections in adults with psoriasis. Therefore, sensitivity analyses were also performed using only hospitalizations with either a primary and/or secondary diagnosis of psoriasis (ICD-9-CM code 696.1) as controls. This allowed for comparison of the relative effect-size of the association between serious infections in AD-E vs. psoriasis. Serious infections were defined as infections which lead to hospitalization, were life threatening, or required

treatment in an inpatient setting. Serious infections were identified using ICD-9-CM or Clinical Classification Software (CCS) codes provided in NIS (eTable 1).

Data processing and statistical analysis

All data analyses and statistical processes were performed using SAS version 9.4 (SAS Institute, Cary, NC). Analyses were performed using SURVEY procedures. The unit of analysis was an individual hospitalization. All statistical models included discharge trend weights, sample strata that account for hospital's census region or division, ownership/control, location/teaching and number of beds that were provided by NIS and clustering by individual hospital. Weighted frequency, prevalence (95% confidence intervals [CI]) of either a primary or secondary diagnosis of a serious infection was determined among patients with and without a primary or secondary diagnosis of AD-E. The hospital cost for inpatient care was calculated based on the total charge of the hospitalization and the cost-to-charge ratio estimated by HCUP. All costs were adjusted for inflation to the year 2014 according to the Consumer Price Index from the US Bureau of Labor Statistics¹⁵. Summary statistics were generated for each infection, including frequency, prevalence and 95% confidence interval (CI), as well as geometric-mean length of stay (LOS), inflation-adjusted cost-of-care, including sum, geometric-mean and 95% CI for hospitalizations with a diagnosis of a serious infection.

Survey logistic regression models were used to determine the association of AD-E and serious infections. The dependent variable was a diagnosis of serious infection vs. no serious infection. The independent variable was a diagnosis of AD-E. Crude odds ratios (OR) and 95% CI were estimated. OR represents the odds of having a diagnosis of a serious infection in those with vs. without a diagnosis of AD-E, where odds is the prevalence of a condition expressed as a percent divided by 1 minus that prevalence. Two different multi-variable models were calculated. Model-1 included age (continuous), sex (male/female), race (white/non-white) and insurance status (yes/no). Model-2 included asthma and hay fever (yes/no).

Severity of AD-E was not available in NIS. Previous studies showed that AD patients with EH have more severe Th2-polarized disease and higher prevalence of food allergies and asthma¹⁶. Therefore, we constructed regression models that included AD-E, EH and a two-way interaction term between them as predictors of sufficiently powered infectious outcomes. Interactions were only included in final models if P-value<0.01 and modification of estimates by >20%.

In order to determine the associations of serious infections in inpatients with AD-E, multi-variable logistic regression models were also constructed by invoking the stepwise selection approach to decide whether to include specific independent variables in the step-wise logistic model (alpha=0.1). Serious infections was the dependent variable. The covariates analyzed were age (18-39/40-59/60-79/ 80), sex (female/male), season of admission (spring/winter/fall/summer), race/ethnicity (white/black/Asian/Hispanic/other or multiracial), median annual income of the hospital ZIP code (quartiles), hospital location (metropolitan > 1 million/fringe/metropolitan <1 million/micropolitan/not metropolitan or micropolitan), insurance coverage (Medicaid/Medicare, private/self-pay/no charge/other), number of chronic conditions (0-1/2-5/6+), hospital region (northeast/midwest/south/west),

bed size (small/medium/large), teaching status (yes/no), diabetes mellitus (AHRQ pre-coded), obesity (AHRQ pre-coded), asthma, and hay fever.

Survey weighted linear regression was performed with log-transformed (2) cost of care or (3) length of stay (LOS) as the dependent variables, in order to determine the impact of serious infections on cost of hospitalization and LOS in AD-E patients. Cost of care and LOS were log-transformed because they were not normally distributed. The independent variable was a diagnosis of any serious infection vs. no serious infection.

Excess LOS and cost of care for an infection indirectly related to AD-E were estimated by: ((prevalence of that infection in AD-E patients) / (prevalence of that infection in non-AD-E patients)) * (Total hospitalization annual days or costs for that infection in AD patients).

Complete case-analysis was performed. Post-hoc correction for multiple dependent tests was performed by minimizing the false discovery rate with the approach of Benjamini and Hochberg¹⁷ and corrected P values are presented. Two-sided corrected P values less than or equal to 0.05 were considered significant. Uncorrected 95% CI are presented.

Results

Overall, there were 72,108,077 adult discharges captured in the NIS between 2002 and 2012, with 9,290 admissions with AD (weighted frequency: 44,605) and 155,909 with eczema (weighted frequency: 746,486) as defined by ICD-9-CM codes 691.8 and 692.9, respectively. Adults hospitalized with AD-E were older (58.6 ± 0.2 vs. 57.0 ± 0.1 years, respectively), less likely to be female (55.8% vs. 60.5%), more likely to be white (70.5% vs. 69.3%) and more likely to have asthma (13.7% vs. 6.3%) and hay fever (0.002% vs. 0.001%) than those without AD-E (Table 1). Serious infections were diagnosed in 42.1% [95% CI: 41.6–42.6] of all hospitalizations in patients with AD-E, but only 25.4% [95% CI: 25.2–25.6] in patients without AD-E. Among hospitalizations in patients with AD-E and serious infections, 53.3% of all serious infections and 43.4% of all skin infections were secondary diagnoses in patients admitted primarily for their AD-E.

AD and serious infections

In logistic regression models with one of the serious infections taken as the dependent variable and AD-E as the only predictor in the model, i.e. simple logistic regression, AD-E was significantly associated with 32 of the 38 serious infections examined, including 8 of 8 cutaneous infections, 2 of 3 upper respiratory infections, 4 of 6 lower respiratory tract or lung infections, as well as cardiac, brain and bone infections, and gastrointestinal infections (eTable 2). Of note, there was significant statewide variation of methicillin-resistant *S aureus* (MRSA) infections ($P = .0002$; eFigure 1).

In multi-variable models controlling for age, race/ethnicity, gender and insurance status, AD-E was significantly associated with any serious infection (adjusted OR [95% CI]: 2.18 [2.14–2.23]). Cutaneous infections with the largest effect size included: EH (67.93 [47.93–96.28]), erysipelas (11.15 [9.47–13.1]) and cellulitis (4.53 [4.42–4.64]). The respiratory infections with highest odds, included aspergillosis, allergic bronchopulmonary aspergillosis

or aspergillosis pneumonia (1.51 [1.21–1.88]), acute pharyngitis (2.19 [1.98–2.41]), acute sinusitis (1.50 [1.34–1.68]), and tuberculosis (1.57 [1.41–1.76]). AD-E was also associated with many other extra-cutaneous and systemic infections, including encephalitis (1.65 [1.40–1.96]), endocarditis (1.25 [1.12–1.39]), infectious arthropathy (2.01 [1.84–2.20]), enterocolitis (1.27 [1.22–1.33]), methicillin-sensitive (MSSA; 2.50 [2.41–2.59]) and methicillin-resistant *Staphylococcal aureus* (MRSA) (3.29 [3.17–3.42]), fungal (3.87 [3.70–4.04]) and viral infections (2.19 [2.10–2.28]), and septicemia (1.27 [1.23–1.32]) (Figure 1, eTable 2). In addition, the associations remained significant for all infections found to be significant in the respective simple logistic regression models except pneumonia and influenza in multi-variable models that controlled for asthma and hay fever (eTable 2). In addition, regression models that included interactions of AD-E with asthma and/or hay fever found that AD-E alone was associated with 32 of 38 infections, whereas AD-E and comorbid asthma and/or hay fever was associated with 24 of 38 infections (eTable 3). Similar results were observed in sensitivity analyses of AD alone (eTables 4 and 5).

Previous studies have shown that psoriasis, another chronic inflammatory skin disease, is associated with higher prevalence of infections. We sought to compare the prevalence of infections in AD-E vs. psoriasis in sensitivity analyses. Similar to AD-E, among hospitalizations in patients with psoriasis and serious infections, 52.9% of all serious infections and 47.4% of all skin infections were secondary diagnoses in patients admitted primarily for their psoriasis.

AD-E was associated with significantly higher odds of 22 of 38 infections examined when compared with psoriasis, including EH, erysipelas, cellulitis, herpes simplex and zoster, acute pharyngitis, bronchitis, endocarditis, MSSA, MRSA, infection with strep, pseudomonas, mycobacterium, fungus, virus, and septicemia (eTable 6). The associations remained significant in multi-variable models 1 and/or 2 for all infections significant in bi-variable models. Only infectious arthropathy, diverticulitis, pyelonephritis, and peritonitis/intestinal abscess were more likely to occur in psoriasis. Similar results were found in sensitivity analyses of AD vs. psoriasis (eTable 7).

In logistic regression models, significant interactions were found between AD-E and EH as predictors of several infections. Patients hospitalized with AD-E and no EH had significantly higher odds of cellulitis (1.79 [1.52–2.11]), erysipelas (21.38 [14.90–30.69]), acute sinusitis (6.63 [4.03–10.90]), and pyelonephritis (4.15 [2.52–6.83]). However, patients with AD-E and EH had an even higher odds of cellulitis (3.56 [2.65–4.78]) (eTable 8).

Associations of serious infections in AD

In multi-variable models with stepwise selection, predictors of any serious infection in patients with AD-E, included increasing age (40–59: 1.36 [1.34–1.38]; 60–79: 1.52 [1.49–1.55]; 80: 2.18 [2.13–2.23]), Hispanic ethnicity (1.07 [1.05–1.09]), lowest median household income (quartile-1: 1.04 [1.03–1.06]), insurance status (Medicare: 1.28 [1.26–1.30]; Medicaid: 1.24 [1.21–1.26]; self-pay: 1.25 [1.21–1.28]; no charge: 1.29 [1.19–1.40]; other: 1.07 [1.03–1.10]), the Southern (1.05 [1.03–1.07]) US regions, the fall (1.06 [1.04–1.07]), summer (1.04 [1.03–1.06]), and winter seasons (1.02 [1.01–1.04]), comorbid diabetes mellitus (1.18 [1.17–1.20]), obesity (1.35 [1.33–1.37]), but inversely associated

with female gender (0.95 [0.94–0.96]), non-white race/ethnicity (Black: 0.94 [0.92–0.95]; Asian: 0.92 [0.89–0.95], other/multiracial: 0.92 [0.89–0.95]), higher number of chronic conditions (2–5: 0.83 [0.81–0.85]; 6: 0.85 [0.83–0.86]), Northeastern (0.89 [0.88–0.90]) and Midwestern (0.95 [0.94–0.97]) US regions, hospital bed size (medium: 0.93 [0.91–0.94]; large: 0.91 [0.89–0.93]), and teaching hospital (0.87 [0.86–0.88]; Table 2). Among patients with AD-E, the prevalence of any serious infections remained stable between 2002–2007 ($P>0.05$) but increased from 2008–2012 when compared to 2002–2003 ($P=0.0002$) (Figure 2). Similar results were found in sensitivity analyses of AD alone (eTable 9).

Impact of serious infections on LOS

The geometric-mean LOS of patients with AD-E and any serious infection (5.3 [5.2–5.3]) was significantly higher than that of patients with AD without any serious infection (3.9 [3.9–4.0]; ANOVA, $P=0.0002$) and significantly higher than those with a serious infection without AD (5.0 [5.0–5.0]; $P=0.0002$) (Table 3). Many cutaneous, respiratory, systemic and multi-organ infections were associated with a prolonged LOS compared with patients without any serious infections (eTable 10). There were an estimated 6,975 excess days spent in the hospital for serious infections in patients with AD, and 138,942 excess days in those with AD or eczema. Cellulitis, any skin infection, pneumonia, strep infections, septicemia, urinary tract infections, and fungal infection accounted for the most excess days associated with infections in inpatients with AD-E.

Impact of serious infections on cost of care

The geometric-mean cost of inpatient care for patients with AD and any serious infection (\$8,273 [\$8,126–\$8,423]) was significantly higher than for patients with AD without serious infection (\$7,179 [\$7,052–\$7,307]); ANOVA, $P=0.0002$) (Table 3). Many cutaneous, respiratory, systemic and multi-organ infections were associated with a higher geometric-mean cost than in patients without any serious infections (eTable 10). There were estimated \$227,618,460 excess costs of hospital care annually for serious infections in patients with vs without AD-E, with cellulitis, any skin infection, pneumonia, urinary tract infections, septicemia and fungal infection accounting for the most excess costs associated with infections. There was a strong correlation between the total annual LOS and cost of care among serious infections in AD-E patients (Spearman correlation, $\rho=0.993$). The excess costs of hospital care for serious infections was \$11,062,120 annually when including patients with AD alone.

Impact of serious infections on inpatient mortality

Patients with AD-E and any serious infection experienced higher rates of inpatient mortality (95% CI) in comparison to AD-E patients without any serious infection (1.7% [1.6–1.8] vs 0.6% [0.6–0.7], $P=0.0002$), including necrotizing fasciitis (2.7% [0.0–5.7]), pneumonia (4.2% [3.8–4.5]), tuberculosis (2.2% [0.8–3.6]), abscess of lung or mediastinum (3.3% [0.0–7.0]), empyema (6.7% [3.1–10.3]), encephalitis (2.8% [0.4–5.3]), endocarditis (4.5% [2.4–6.4]), enterocolitis (2.9% [2.2–3.5]), *clostridium difficile* (3.8% [3.0–4.7]), peritonitis and intestinal abscess (3.9% [2.3–5.5]), urinary tract infections (1.9% [1.7–2.1]), MRSA (2.1% [1.6–2.5]), pseudomonas infection (2.2% [1.5–2.8]), mycobacterial infection (3.1% [0.4–5.8]), influenza (2.1% [0.4–3.8]), and septicemia (6.9% [6.3–7.4]) (Table 3, eTable 10).

Discussion

This study demonstrated that adults with AD and/or eczema as judged by ICD-9-CM codes 691.8 and 692.9, respectively, had significantly higher prevalences of serious infections compared to those without AD, including infections of the skin, lower respiratory tract and lungs, heart, brain, gastrointestinal tract, and bones. Approximately 1 in 2 serious infections overall and skin infections in particular were secondary diagnoses in adults admitted primarily for AD. Higher prevalences of multiple infections occurred in AD vs. psoriasis. Further, prevalence of cellulitis was even higher in AD patients with EH compared with those who had AD alone. Further, higher prevalence of serious infections occurred in AD patients who were older, male, white, had lower household income, and public or no insurance. These results are consistent with previous studies that found higher rates of both cutaneous and extra-cutaneous infections in AD^{7, 12, 13}. A US population-based study of 91,642 children from the National Survey of Children's Health found the children with AD had significantly higher rates of recurrent ear infections¹². Another US population-based study of 9,417 children from the National Health Interview Survey found that children with AD had significantly higher rates of cutaneous warts, as well strep throat, other sore throat, head or chest cold, influenza or pneumonia, sinus infections, recurrent ear infections, chickenpox and urinary tract infections⁷. A study of 34,613 adults from the National Health Interview Survey found that adults with AD had significantly higher prevalences of influenza or pneumonia, strep throat, head or chest cold, sinus infection, gastroenteritis, chickenpox, infectious diseases or other immune problems and fever lasting more than 24 hours¹³. Together, there appear to be higher rates of extra-cutaneous and systemic infections in both children and adults with AD.

The results of the present study are consistent with prior studies that examined associations between AD and serious infections based on surveys utilizing questions about self- or caregiver- reported AD and serious infections. In contrast, the present study examined the associations between AD and serious infections that were diagnosed and recorded by a healthcare professional. Furthermore, this study examined serious infections that were not previously examined and illustrated data on utilization related to these comorbidities including hospitalization rates, cost of care, length of stay, and mortality further illustrating the indirect costs and financial burden of AD.

The financial-burden of serious infections in patients with AD was substantial. Thirty-seven of 38 serious infections were associated with increased LOS of hospitalization and 31 of 38 with higher costs of care, when compared to adults with AD and no serious infection. AD was indirectly associated with \$11-\$228 million of excess healthcare costs annually for hospitalization from serious infections. Some older studies estimated the direct-costs of AD to be \$364 million to \$3.8 billion US dollars per-year¹⁸. The present study indicates that there are increased indirect healthcare costs and mortality related to the comorbid health conditions of AD, such as infections. These results beg for future interventions aimed at lowering the prevalence and improving the management of serious infections in patients with AD.

The infections associated with highest inpatient mortality in patients with AD were septicemia (6.9%) followed by empyema, endocarditis, pneumonia, peritonitis and intestinal abscess, *Clostridium difficile* infection, abscess of lung and mediastinum, mycobacterial infection, enterocolitis, encephalitis, MRSA, and MSSA. The increased prevalence and inpatient mortality of AD patients secondary to MRSA and other bacterial infections raise concerns about the antibiotic treatment in AD and antibiotic-resistance. Topical and oral antibiotics are often used for the treatment of AD, despite a lack of evidence supporting their efficacy as a treatment for uninfected AD¹⁹. Excess use of antibiotics may contribute to higher rates of antibiotic-resistance and expose AD patients to higher risk of mortality from MRSA. The current guidelines recommend antibiotics only be used for the treatment of clinically infected AD¹⁹.

The mechanisms of increased multi-organ and systemic infections are unknown. Epidermal barrier dysfunction⁹ decreased expression of anti-microbial peptides in skin¹⁰ have been suggested to predispose toward cutaneous infections. Further, previous studies showed that AD severity is highly correlated with levels of *Staphylococcus aureus* colonization of skin^{20, 21}. In addition, recent studies demonstrated aberrant toll-like receptor signaling and innate immunity in AD^{11, 22}. It is possible that barrier disruption, increased bacterial colonization, and immune dysregulation facilitate trans-cutaneous penetration of pathogens, thereby becoming a nidus for systemic infection. Recent studies also found evidence of profound systemic inflammation in AD patients^{23, 24} and multiple comorbid health conditions²⁵. Some of the respiratory infections might be due to comorbid asthma and/or atopic disease. However, most of the associations remained significant even in multi-variable models that controlled for asthma and hay fever (Model-2). It has been proposed that AD is a systemic disease²⁵. Thus, topical and/or systemic agents that successfully improve barrier dysfunction and immune regulation in both the skin and systemically, and reduce *Staphylococcal* colonization, might subsequently reduce the association of AD with serious infections. On the other hand, the systemic medications most commonly used in North America for the treatment of AD, including corticosteroids, cyclosporine, methotrexate, and mycophenolate mofetil²⁶, are highly immunosuppressing and may contribute to the higher prevalence of systemic infections. Large quantities of topical corticosteroids and/or calcineurin inhibitors may also impact infectious risk. Use of narrower target-driven systemic or biological agents may have the benefit of not increasing risk of infection. Future research is needed to determine the mechanism(s) of association with systemic infections in AD patients and optimal approaches toward reducing these associations.

The strengths of this study include a nationally representative sample of >87 million hospitalizations spanning eleven years. We previously found code 691.8 to be sufficiently valid for identifying AD in the inpatient setting¹⁴. We also found that the ICD-9-CM codes for AD (691.8) and eczema (692.9) are used interchangeably, with similar proportions of patients meeting diagnostic criteria for AD⁸ whether they were coded as AD or eczema¹⁴. Thus, primary analyses of associations with serious infections were performed for AD and/or eczema. Estimates of excess costs associated with infection were performed in hospitalizations with AD alone, as well as AD or eczema combined. The use of different ICD codes for AD is due largely from the imprecision in nomenclature used for the disease, e.g. atopic dermatitis, atopic eczema, eczema, etc {Kantor, 2016 #2866; Xu, 2017

#2881;Hsu, 2016 #3456}. Further, the term “eczema” is associated with the ICD-9-CM code for contact dermatitis (692.9), rather than the one for AD or AE (691.8). This issue will likely remain a problem with ICD-10, where “eczema” is associated with ICD-10 code for rash not otherwise specified (L30.9). Standardization of terminology that is in-line with the current ICD code definitions is essential in order to address this imprecision of nomenclature and resultant use of ICD codes. The International Eczema Council recently reached consensus, recommending use of the prefix "atopic" (i.e., atopic dermatitis or atopic eczema, but not eczema alone) {Silverberg, 2017 #3538}. Consistent use of this more precise terminology is likely to improve the validity of using ICD codes to identify AD in claims datasets; though, this may take many years to reach fruition. We were unable to determine the department of hospitalization, e.g. dermatology vs. non-dermatology. It is possible that the association of AD and serious infections differs based on department of hospitalization. However, few US hospitals have dedicated dermatology wards. Most patients hospitalized with a dermatologic disorder would be admitted to a non-dermatology ward. NIS did not record the dates of assigned diagnoses, which precluded assessment of whether the serious infections began before or during hospitalization. Moreover, we were unable to determine how many of the hospitalizations were due to readmissions or transfers between hospitals. It is possible that some patients were admitted repeatedly for infections. Finally, because manual chart review was not possible, prior patient history was not available and the study was limited by our inability to assess the severity or phenotype of AD, history of immunodeficiency, outpatient treatment approaches, e.g. oral immunosuppressive medications, and how these may have impacted the prevalence of serious infections. We did find that AD patients with vs. without EH had even higher odds of cellulitis. This suggests that more severe AD has even higher odds of infection than mild AD. Alternatively, EH may be a sign of a particular subset of AD patients that are vulnerable to infections. Future studies are needed to determine their impact on serious infections.

In conclusion, adults with AD had significantly higher odds of cutaneous, respiratory, multi-organ and systemic infections. Serious infections were associated with a substantial financial-burden in patients with AD. Further studies are needed to understand the mechanisms of extra-cutaneous and systemic infections in AD and develop interventions to prevent them.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Support: This publication was made possible with support from the Agency for Healthcare Research and Quality (AHRQ), grant number K12 HS023011, the Dermatology

Abbreviations used

AD	atopic dermatitis
AD-E	Atopic dermatitis or eczema

ICD-9-CM International Classification of Disease 9th edition Clinical Modification

LOS length of stay

NIS Nationwide Inpatient Sample

OR odds ratio

CI confidence interval

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Figure 1.

Association between AD-E and serious infections. Survey logistic regression models were constructed with AD-E as the independent variable and the respective serious infection as the dependent variable. Models included age, gender, race/ethnicity, and insurance status as covariates. Adjusted odds ratios and 95% confidence intervals were estimated. Forest-plots of the adjusted odds ratios and 95% confidence intervals are presented.

Figure 2. Prevalence of serious infections in hospitalized patients with AD (squares) vs. without AD (circles)

Proportion of hospitalized patients with AD (squares) and without AD (circles) is plotted over time (2002–2003, 2004–2005, 2006–2007, 2008–2009, 2010–2012).

Table 1

Patient demographics.

Variable	Atopic dermatitis or eczema (AD-E)	
	No	Yes
Age (yr) (SEM)	57.0 (0.1)	58.6 (0.2)
Female – freq (%)	206,858,933 (60.5%)	440,151 (55.8%)
Race – freq (%)		
White	189,154,066 (69.3%)	454,630 (70.5%)
Black	38,343,543 (14.0%)	103,415 (16.0%)
Asian	6,318,149 (2.3%)	18,153 (2.8%)
Hispanic	29,487,232 (10.8%)	47,774 (7.4%)
Multiracial/Other	9,752,857 (3.6%)	21,257 (3.3%)
Asthma–freq (%)	21,405,851 (6.3%)	108,348 (13.7%)
Hay fever–freq (%)	2,513 (0.001%)	13 (0.002%)

Table 2

Associations of serious infections in adults with atopic dermatitis or eczema.

Variable	Adjusted OR [95% CI]	P Value
Age (yr)		
18–39	1.00 [ref]	-
40–59	1.36 [1.34–1.38]	.0002
60–79	1.52 [1.49–1.55]	.0002
80	2.18 [2.13–2.23]	.0002
Gender		
Female	0.95 [0.94–0.96]	.0002
Male	1.00 [ref]	-
Race		
White	1.00 [ref]	-
Black	0.94 [0.92–0.95]	.0002
Hispanic	1.07 [1.05–1.09]	.0002
Asian	0.92 [0.89–0.95]	.0002
Other	0.92 [0.89–0.95]	.0002
Income Quartile		
1	1.04 [1.03–1.06]	.0002
2	1.01 [0.99–1.02]	.5
3	1.00 [0.99–1.02]	.9
4	1.00 [ref]	-
Insurance		
Medicare	1.28 [1.26–1.30]	.0002
Medicaid	1.24 [1.21–1.26]	.0002
Private	1.00 [ref]	-
Self-pay	1.25 [1.21–1.28]	.0002
No charge	1.29 [1.19–1.40]	.0002
Other	1.07 [1.03–1.10]	.002
No. of chronic conditions [#]		
0–1	1.00 [ref]	-
2–5	0.83 [0.81–0.85]	.0002
6	0.85 [0.83–0.86]	.0002
Region		.0002
Northeast	0.89 [0.88–0.90]	.0002
Midwest	0.83 [0.81–0.85]	.0002
South	1.05 [1.03–1.07]	.0002
West	1.00 [ref]	-
Season		

Variable	Adjusted OR [95% CI]	P Value
Fall	1.06 [1.04–1.07]	.0002
Summer	1.04 [1.03–1.06]	.0002
Winter	1.02 [1.01–1.04]	.01
Spring	1.00 [ref]	-
Hospital Location		
Metro > 1 mill	1.00 [ref]	-
Fringe/metro < 1 mill	0.95 [0.93–0.96]	.0002
Micropolitan ^{##}	0.95 [0.93–0.97]	.0002
Not metro or micropolitam	0.93 [0.91–0.96]	.0002
Hospital Bed Size		
Small	1.00 [ref]	-
Medium	0.93 [0.91–0.94]	.0002
Large	0.91 [0.89–0.93]	.0002
Hospital Teaching Status		
Non-teaching	1.00 [ref]	-
Teaching	0.87 [0.86–0.88]	.0002
Comorbidity		
Diabetes Mellitus	1.18 [1.17–1.20]	.0002
Obesity	1.35 [1.33–1.37]	.0002
Asthma	0.95 [0.94–0.97]	.0002

^aChronic conditions were defined by HCUP as lasting 12 months or longer and meeting 1 or both of the following: (1) places limitations on self-care, independent living, and social interactions and/or (2) results in the need for ongoing intervention with medical products, services, and special equipment. Chronic condition count was calculated and provided by HCUP.

^bMore than or equal to 1 urban cluster of population of 10,000 to 49,999.

Table 3

Costs of care, length of stay, and inpatient mortality of adults with atopic dermatitis or eczema and serious infections.

Serious infection	Geometric-mean cost in patients with AD-E [95% CI]	Excess annual cost secondary to AD-E	Excess annual cost secondary to AD	Geometric-mean LOS in patients with AD-E (days) [95% CI]	Excess annual LOS secondary to AD-E	Excess annual LOS secondary to AD	Inpatient mortality in patients with AD-E [95% CI]
None	\$7,179 [\$7,052-\$7,307]	-	-	3.9 [3.9-4.0]	-	-	0.6 [0.6-0.7]
Any	\$8,273 [\$8,126-\$8,423]	\$227,618,459.9	\$11,062,119.96	5.3 [5.2-5.3]	138,941.67	6,974.68	1.7 [1.6-1.8]

Abbreviations: AD, atopic dermatitis; CI, confidence interval