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

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ABSTRACT

Background: Atopic dermatitis (AD) is associated with barrier disruption, immune dysregulation, and immunosuppressing treatments that can increase the association with an unusual number of infections.
Objective: To determine whether adults with AD have an unusually large number of serious infections and related outcomes.
Methods: Data from the 2002 to 2012 National Inpatient Sample were analyzed, including an approximately 20% sample of all US hospitalizations (n = 72,108,077 adults). Prevalence of serious infections in hospitalized patients with vs without AD, length of stay, cost of care, and inpatient mortality secondary to serious infections were determined.
Results: The prevalence of serious infections expressed as a percentage (95% confidence interval) was higher in adults hospitalized with than in those without AD (42.1% [41.6–42.6] vs 25.4% [25.2–25.6]; $P = .0002$). In logistic regression models with multiple predictors (multivariable logistic regression models), AD was associated with 32 of 38 infections examined. Associated cutaneous infections included eczema herpeticum (odds ratio [95% confidence interval] adjusted for other predictors: 67.93 [47.93–96.28]), erysipelas (11.15 [9.47–13.1]), and cellulitis (4.53 [4.42–4.64]). Associated respiratory infections included aspergillosis (1.51 [1.21–1.88]) and tuberculosis (1.57 [1.41–1.76]). AD was associated with extracutaneous, multiorgan, and systemic infections, including infectious arthropathy (2.01 [1.84–2.20]), endocarditis (1.25 [1.12–1.39]), encephalitis (1.65 [1.40–1.96]), and methicillin-resistant *Staphylococcus aureus* infections (3.29 [3.17–3.42]). Patients with AD hospitalized with vs without any serious infection had an increased geometric mean cost of inpatient care ($8,273 [8,126–8,423] vs $7,179 [7,052–7,307]) and length of stay (5.3 days [5.2–5.3] vs 3.9 [3.9–4.0]; $P = .0002$), with $11 to $228 million excess annual costs from hospitalization with serious infections in adults with AD.
Conclusion: Adults with AD had increased cutaneous, respiratory, multiorgan, and systemic infections, which were associated with a considerable cost burden.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting 13% of children[1] and 7% to 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, eczema herpeticum (EH),[4–6] and possibly cutaneous warts.[7] In fact, predisposition toward cutaneous infection is one of the minor diagnostic criterion for AD according to Hanifin and Rajka.[8] The mechanism of such predisposition is believed to be multifactorial, including impaired epidermal barrier function,[9] decreased expression of antimicrobial peptides,[10] and an abnormal innate immune response in skin.[11]

Recent US population-based studies have shown that AD also is associated with higher rates of extracutaneous infection in children[7,12] and adults,[13] such as infections of the upper and lower respiratory tracts, ears, and urinary tract. Those studies used 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 health care-diagnosed AD and serious infections in adults. We hypothesized that adults with AD would have significantly higher prevalences of cutaneous, respiratory, multiorgan, and systemic infections.

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Methods

Data Source

The 2002 to 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 the NIS contains an approximately 20% stratified representative cross-sectional sample of all US hospitalizations. Sample weights were created by the NIS that factored the sampling design of hospitals in the United States. These sample weights allow for representative estimates of hospital discharges across the entire 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 the NIS were compliant to the HCUP's formal data use agreement. The study was approved by the institutional review board at Northwestern University (Chicago, Illinois).

Identification of AD and Serious Infections

The databases were searched for a primary and/or secondary diagnosis of AD or eczema using *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 AD.[14] 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 patients with AD being coded as having eczema.[14] 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 length of stay (LOS) estimates, recognizing that analysis of AD alone would underestimate the true prevalence and that analysis of AD-E could 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 have reported higher rates of serious infections in adults with psoriasis. Therefore, sensitivity analyses also were performed using only hospitalizations with 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 that led to hospitalization, were life threatening, or required treatment in an inpatient setting. Serious infections were identified using *ICD-9-CM* or Clinical Classification Software codes provided in the NIS (eTable 1).

Data Processing and Statistical Analysis

All data analyses and statistical processes were performed using SAS 9.4 (SAS Institute, Cary, North Carolina). Analyses were performed using SURVEY procedures. The unit of analysis was an individual hospitalization. All statistical models included discharge trend weights, sample strata that accounted for a hospital's census region or division, ownership and control, location and teaching status, number of beds that were provided by the NIS, and clustering by individual hospital. Weighted frequency and prevalence (95% confidence intervals [CI]) of a primary or secondary diagnosis of a serious infection were 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 the HCUP. All costs were adjusted for inflation to 2014 according to the Consumer Price Index from the US Bureau of Labor Statistics.[15] Summary statistics were generated for each infection, including frequency, prevalence and 95% CI, geometric mean LOS, and inflation-adjusted geometric mean cost of care, including sum and geometric mean and 95% CI for hospitalizations with a diagnosis of a serious infection.

SURVEY logistic regression models were used to determine the association between 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 (ORs) and 95% CIs were estimated. OR represents the odds of having a diagnosis of a serious infection in those with vs without a diagnosis of AD-E, whereas odds is the prevalence of a condition expressed as a percentage divided by 1 minus that prevalence. Two different multivariable models were calculated. Model 1 included age (continuous), sex (male vs female), race (white vs nonwhite), and insurance status (yes vs no). Model 2 included asthma and hay fever (yes vs no).

Severity of AD-E was not available in the NIS. Previous studies have shown that patients with AD and EH have more severe T-helper cell type 2–polarized disease and a higher prevalence of food allergies and asthma.[16] Therefore, we constructed regression models that included AD-E, EH, and a 2-way interaction term between them as predictors of sufficiently powered infectious outcomes. Interactions were included in the final models only when the *P* value was less than .01 and the modification of estimates was greater than 20%.

To determine the associations of serious infections in inpatients with AD-E, multivariable logistic regression models were constructed by invoking the stepwise selection approach to decide whether to include specific independent variables in the stepwise logistic model ($\alpha = 0.1$). Serious infection was the dependent variable. The covariates analyzed were age (18–39, 40–59, 60–79, ≥80 years), sex (female vs 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 or 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 or no), diabetes mellitus (AHRQ pre-coded), obesity (AHRQ pre-coded), asthma, and hay fever.

SURVEY weighted linear regression was performed with logarithmically transformed cost of care or LOS as the dependent variables to determine the impact of serious infections on cost of hospitalization and LOS in patients with AD-E. Cost of care and LOS were logarithmically 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 patients with AD-E]/[prevalence of that infection in patients without AD-E]) × (total hospitalization annual days or costs for that infection in patients with AD).

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 Hochberg[17] and corrected *P* values are presented. Two-sided corrected *P* values less than or equal to .05 were considered significant. Uncorrected 95% CI are presented.

Results

Overall, there were 72,108,077 adult discharges captured in the NIS from 2002 to 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 women (55.8% vs