INTRODUCTION

Atopic dermatitis (AD) is associated with considerable morbidity and quality of life impairment (Drucker et al., 2017). Patients with AD may require hospitalization for severe intermittent flares or persistent disease refractory to outpatient treatment, sometimes in association with psychiatric comorbidity or inability to properly self-care. However, little is known about the inpatient financial burden of AD in the United States.

The prevalence of AD has increased globally over the past few decades (Deckers et al., 2012). Approximately 13% of US children have AD, of whom one-third have moderate-severe disease (Silverberg and Simpson, 2013, 2014); 7–10% of US adults have AD (Silverberg et al., 2015; Silverberg and Hanifin, 2013). High prevalences and associated morbidity account for AD being the skin disease with highest disability-adjusted life-years in the 2010 Global Burden of Disease project (Murray et al., 2012; Vos et al., 2012) and considerable cost of care. Older estimates of direct payer costs of AD were $364 million (Lapidus et al., 2012) and $3.8 billion (Ellis et al., 2002) per year.

Given the rise in AD prevalence in the United States over the past 2 decades and large proportion of adults with AD, it is likely that costs of care have increased concomitantly. In addition, the cost burden of hospitalization for AD has not been explored. Overall, only 7% of the US population had an inpatient hospital stay in 2011, which accounted for 29% of all health care expenses, making hospitalization one of the most expensive types of health care treatments (Moore et al., 2006). Interventions aimed at reducing hospitalization for AD may reduce health expenditures and the public-health burden of AD. In the present study, we analyzed the prevalence of length of stay (LOS) and cost of care for hospitalization for AD in the United States.

RESULTS

Hospitalization prevalence and trends

Overall, there were 87,053,155 discharges in the National Inpatient Sample (NIS) between 2002 and 2012. There were 6,577 admissions for AD or eczema (AD-E), including 4,330 adults and 2,247 children (weighted frequency: 31,380, 20,705, and 10,675, respectively). The prevalence of hospitalization ranged from 58–76, 431–527, and 86–105 per million hospitalized adults, children, or both, respectively. In children, the frequency of hospitalization was highest at ages 0–1 years, decreased during childhood and adolescence, and remained stable throughout adulthood (Figure 1).

Patients admitted with a primary diagnosis of AD-E had a significantly higher prevalence of asthma than those without AD-E (24.8% and 11.0% vs. 7.3%; P = 0.0004 for both). This was true for adults (26.3% and 9.8% vs. 6.8%; P = 0.0004 for both) and children (23.9% and 14.6% vs. 13.8%; P = 0.0004 and 0.6, respectively). Patients admitted with a primary diagnosis of AD-E had higher prevalences of viral (adults: 2.1% vs. 0.9%; children: 5.2% vs. 4.7%), bacterial (adults: 9.6% vs. 5.8%; children: 33.3% vs. 6.1%), and any skin infections (adults: 18.9% vs. 4.3%; children: 32.3% vs. 3.7%) than those without AD-E (P = 0.0004 for all).

The prevalences of hospitalization for AD-E were higher in adults in 2006–2007, 2008–2009, 2010–2011, and 2012 compared with 2002–2003 (P ≤ 0.01 for all) (Figure 2a), but not in children (Figure 2b). Similar results were observed for eczema alone. However, there were no significant differences of the prevalence of hospitalization for AD between 2002 and 2012.
Overall, prevalences of hospitalization for AD-E were highest in spring and summer for adults and children (Table 1).

Hospitalization rates (95% confidence interval [CI]) for AD-E were highest in the south (37.3% [34.0–40.6%]), followed by the midwest (23.9% [20.8–27.0%]) and northeast (23.1% [20.6–25.6%]), and least in the west (15.7% [13.5–18.0%]). Similar regional patterns were observed in adults and children and in models of AD or eczema alone (Supplementary Tables S1 and S2 online). Hospitalization rates for AD-E were highest in the northeast and lowest in the south during the winter, but highest in the south and lowest in the northeast during the summer.

In adults, there were significantly higher odds of hospitalization for AD-E in the northeast (bivariate logistic regression; odds ratio [95% CI]: 1.47 [1.26–1.71]) and midwest (1.28 [1.09–1.50]). Similar results were found for adults with eczema, but no associations between region and hospitalization for AD-E were observed in children. However, pediatric eczema was associated with higher odds of hospitalization in the south (1.47 [1.15–1.87]) and northeast (1.38 [1.07–1.78]). There were no associations between region and hospitalization for AD in children or adults.

Disposition
The majority of adults with AD-E were classified into minor (70.8%) or moderate (23.5%) likelihood of dying by All Patient Refined Diagnosis-Related Group, whereas almost all children were classified into minor (97.5%) likelihood of dying. Loss of function severity was most commonly minor (adults: 36.3%; children: 59.8%) and moderate (adults: 48.7%; children: 33.8%). The majority of adults (79.7%) and children (96.6%) were discharged routinely (Table 2). Similar results were found in the analyses of AD or eczema alone (Supplementary Table S3 online).

LOS
LOS in the hospital was significantly shorter in adults and children with versus without a primary diagnosis of AD-E (geometric-mean [95% CI] for adults: 2.7 [2.7–2.8] vs. 3.5 [3.5–3.5] days; children: 2.4 [2.3–2.5] vs. 2.7 [2.7–2.7] days; P = 0.0004) (Figure 2c and d). Similar results were found in adults and children with diagnoses of AD or eczema alone.

Cost of care
The total inflation-adjusted cost of care for hospitalization with a primary diagnosis of AD-E was $127,841,466 (adults: $8,288,083 per year; children: $3,333,868 per year). Note that the actual cost is actually higher because 55 observations had missing values for charge and/or cost.
AD-E versus neither was $3,502 [\$3,360–\$3,680] for adults and $2,716 [\$2,903–\$2,542] versus $2,716 for children (Hsu et al., 2015, 2016b). In the United States, hospitalization for AD-E were due to 62.5% and 50% shorter LOS than previously observed in psoriasis or pemphigus (Hsu et al., 2015), respectively. The prevalence of hospitalization with a primary diagnosis of AD-E increased in adults between 2002 and 2012, compared with stable or decreasing rates of hospitalization previously observed in psoriasis (Hsu et al., 2016b) and pemphigus (Hsu et al., 2015), respectively. Mean inpatient costs per hospitalization for AD-E were only 60% and 33% of the costs per hospitalization for psoriasis or pemphigus (Hsu et al., 2015, 2016b). Lower costs per hospitalization for AD-E were due to 62.5% and 50% shorter LOS than previously observed for pemphigus and psoriasis (Hsu et al., 2015, 2016b). In the United States, hospitalization primarily for acute care of AD-E is often needed for optimized topical and/or systemic therapy in patients with uncontrolled skin disease in the outpatient setting. Inpatient treatments include topical corticosteroid wet-wraps, requiring more aggressive and skilled nursing care, and initiation of systemic immunosuppressants. Few hospitals have dedicated dermatology wards with specialized nurses. Most patients hospitalized primarily with a dermatologic disorder would be admitted to a general ward. LOS for hospitalization may be shorter for AD-E than psoriasis or pemphigus because of a faster treatment response. The acute signs and symptoms of AD-E, that is, erythema, oozing/weeping, scaling, and pruritus, may resolve faster with optimized treatment than vesicobullae and erosions in pemphigus or “lakes of pus” and skin sloughing in generalized pustular psoriasis. Furthermore, biologic therapies used in severe pemphigus and psoriasis may contribute to increased mean cost per hospitalization compared with AD. Hospitalization for AD was associated with good prognosis, including shorter LOS, few invasive procedures, and only mild-moderate disability. Despite a subset of patients with AD being at increased risk for inpatient mortality, there were virtually no deaths, suggesting that inpatient management successfully mitigated mortality risk. However, because of the higher prevalence of hospitalization for AD, the total inpatient costs for AD were 40% and 70% higher than for psoriasis and pemphigus during the same time period, respectively (Hsu et al., 2015, 2016b). Prevalences and costs of hospitalization for AD significantly increased during the study period without plateauing, indicating that the total cost of inpatient care for AD may continue to increase.

The geometric-mean [95% CI] cost of hospitalization with AD-E versus neither was $3,502 [\$3,360–\$3,680] versus $6,849 [\$6,775–\$6,925] for adults and $2,716 [\$2,542–\$2,903] versus $4,488 [\$4,302–\$4,682] for children. Costs of hospitalization for adults with AD-E were higher in 2010–2011 and 2012 compared with 2002–2003 (P ≤ 0.01) and higher in 2012 compared with 2002–2003 in children (P = 0.01) (Figure 2e and f).

**DISCUSSION**

The present study demonstrates a considerable inpatient financial burden of AD in the United States. Between 2002 and 2012, the prevalence of hospitalization for AD-E was 2.4- and 5.6-fold higher than for psoriasis (Hsu et al., 2016b) and pemphigus (Hsu et al., 2015) during the same time period, respectively. The prevalence of hospitalization with a primary diagnosis of AD-E increased in adults between 2002 and 2012, compared with stable or decreasing rates of hospitalization previously observed in psoriasis (Hsu et al., 2016b) and pemphigus (Hsu et al., 2015), respectively. Mean inpatient costs per hospitalization for AD were only 60% and 33% of the costs per hospitalization for psoriasis or pemphigus (Hsu et al., 2015, 2016b). Lower costs per hospitalization for AD-E were due to 62.5% and 50% shorter LOS than previously observed for pemphigus and psoriasis (Hsu et al., 2015, 2016b). In the United States, hospitalization primarily for acute care of AD-E is often needed for optimized topical and/or systemic therapy in patients with uncontrolled skin disease in the outpatient setting. Inpatient...
There are considerable differences in the delivery and costs of dermatological care in the United States versus other countries. Few studies assessed the economic burden of AD internationally, with the majority focusing on outpatient costs of AD. A Thai study of the costs of early childhood atopic disease found costs of 2.9 billion Thai baht ($94 million USD), including 302 million Thai baht ($9.7 million USD) for AD (Ngamphaiboon et al., 2012). AD costs were posited to be lower because of differences in climate and AD management in Thailand compared with western countries. A retrospective cohort study of AD costs using data from general practitioners and one general hospital in the Netherlands found that most patients were seen by a general practitioner in the outpatient setting and few were referred to the hospital (Verboom et al., 2002). Mean health care costs (adjusted to the 1999 US Consumer Price Index) were $71 per-patient-year, mostly from general practitioner visits ($32 USD) and medications, mostly corticosteroids ($21 USD). Referral to a hospital-based specialist occurred in only 7.8% of patients with AD and was associated with higher costs ($186 USD). Hospitalization for AD was rare, with unspecified costs. Costs of AD care were posited to be low in their cohort because of the low hospitalization rates. A cross-sectional survey of 1,523 parents of British children aged 1–5 years found mean annual costs per child with AD of £79.59, with only £1.96 incurred by caregivers for seeing a private specialist (Emerson et al., 2001). That study did not examine costs of AD hospitalization. A survey study of 85 Australian adolescents and adults with AD found a mean A$425 annual out-of-pocket costs used for treatment (range: A$13.50–A$2105.64) (Jenner et al., 2004). Direct payer costs, hospitalization rates, and costs were not assessed. Another Australian study using modeling and expert opinion found that inpatient costs accounted for more than half of direct costs of AD in infants (Su et al., 2012). A study of 40 Indian children with AD in an outpatient hospital setting found a high number of flares (mean = 3.0) and outpatient hospital visits (mean = 6.5), with high provider costs, including consultation, nursing/paramedical staff, and infrastructure (mean = 948 rupees) (Handa et al., 2015). However, acute inpatient care for AD was not assessed in that study. A UK study of 155 outpatients with AD and 10 patients hospitalized with AD in the previous year found mean health services costs of £16.2 and £415 in 2 months, respectively, with hospital consultations accounting for 6% of health services costs (Herd et al., 1996). There are several challenges of comparing

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Abbreviations: CI, confidence interval; ICF, intermediate care facility; SNF, skilled nursing facility.
costs of hospitalization internationally, including different currencies, periods of study, age groups of patients, and definitions of AD and hospital care. Even among studies that assessed direct costs related to hospitalization, most used modeling of representative patients, but few examined actual disease costs on the population level.

AD hospitalization was highest in regions with cold weather during the fall and winter time, but warm weather during the spring and summer time. These patterns likely reflect the effects of climate and other environmental factors on triggering AD flares. A US population-based study of 91,642 children found the 1-year prevalence of AD to be significantly associated with decreased temperature, humidity, and ultraviolet index, and increased use of indoor heating (Silverberg et al., 2013). A systematic review explored the mechanisms of worsening AD in the wintertime and proposed that low humidity and temperature during the winter impair skin-barrier function and increase susceptibility to mechanical stresses, irritants, and allergens (Engbretsen et al., 2016). A German study suggested that AD may flare seasonally in both the winter, secondary to low outdoor temperatures, and summer, secondary to high outdoor temperature and grass pollen counts (Kramer et al., 2005). Sweating is one of the most commonly reported exacerbants of itch in AD (Williams et al., 2004; Yosipovitch et al., 2002). Furthermore, higher rates of *Staphylococcus aureus* skin infections have been demonstrated globally in warmer regions (Tong et al., 2011). These may have contributed toward AD flares observed in the Southern United States during the summer months. Indeed, patients hospitalized with AD-E had higher rates of cutaneous infections. Further studies are needed to elucidate the interaction between climate, skin flora and infection, and AD flares.

We previously found the code 691.8 to be sufficiently valid for identifying AD in the inpatient setting (Hsu et al., 2016a). We also found that the International Classification of Diseases, Ninth Revision, Clinical Modification codes for AD (691.8) and eczema (692.9) are used interchangeably, with similar proportions of patients meeting diagnostic criteria for AD (Hanifin and Rajka, 1980) whether they were coded as AD or eczema (Hsu et al., 2016a). A study of the top diagnoses at the dermatologist from the 1993 to 2010 National Ambulatory Medical Care Survey found that among patients aged 0–4 years, 18.4% had AD and 16.1% had eczema (Landis et al., 2014). Therefore, we examined both codes and performed sensitivity analyses between codes. Indeed, the code for eczema was used more frequently than the code for AD in all age groups. This is particularly interesting in young children, where other eczematous dermatoses are relatively uncommon compared with AD, such as allergic contact dermatitis and eczematous drug eruptions. It is unlikely that other eczematous etiologies would be confused for AD in young children or that such disorders would commonly result in hospitalization for acute care in any age group. Thus, we believe that most of these cases represent miscoding of AD as eczema. Nevertheless, some patients who were coded with eczema may have had other etiologies of eczematous dermatoses, which may contribute to the particularly high proportion of eczema cases observed at ages 40–59 years. Therefore, estimates for AD-E may overestimate the costs of AD, whereas analyses of AD or eczema alone underestimate the costs. There is heterogeneity of terminology in both the scientific literature (Kantor et al., 2016) and global search engine trends (Xu et al., in press), including AD, eczema, atopic eczema, etc. Future efforts are needed to harmonize the nomenclature of AD to reduce misclassification and coding errors.

Strengths of this study include a nationally representative sample of >87 million hospitalizations spanning 11 years. Weaknesses of this study include the lack of information about the onset, severity and phenotype of AD, or outpatient treatments and how these impacted hospitalization rates and course. We could not determine if the primary diagnosis of AD was given by a dermatologist versus other physician, or what diagnostic criteria were used. Hospitalizations with a primary diagnosis of AD-E indicate that AD-E was the primary reason for admission. However, we could not determine more specific reasons, such as acute-onset severe flares versus persistent severe disease refractory to outpatient treatments. We were also unable to determine how many hospitalizations were due to readmissions. Patients with severe disease or nonadherence to treatment may have had multiple admissions. Nevertheless, readmissions of such patients are appropriately reflected in estimates of LOS and cost of hospitalization.

In conclusion, this study demonstrates a considerable inpatient burden of AD in the United States, with higher prevalence and total costs than other chronic inflammatory skin disorders. Future research is needed to develop clinical and policy interventions to help reduce hospitalization in AD.

**METHODS**

**Data source**

The 2002–2012 NIS was analyzed. The NIS was developed as part of the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality. Each year of the NIS contains an approximately 20% stratified representative sample of all US hospitalizations. All data were deidentified and no attempts were made to identify any of the individuals in the database. All parties with access to the Healthcare Cost and Utilization Project were compliant to Healthcare Cost and Utilization Project’s formal data use agreement. The study was approved by the institutional review board at Northwestern University.

The databases were searched for a primary discharge diagnosis of AD or eczema using the International Classification of Diseases, Ninth Revision, Clinical Modification codes 691.8 (AD) and/or 692.9 (eczema). The NIS defined primary diagnosis as the medical condition principally responsible for the hospitalization of the patient, and was assigned at the time of hospital discharge. Three variables were created for these analyses, including primary diagnosis of AD, eczema, and AD-E. The control group included all hospitalizations without any AD-E and excluded normal pregnancy/delivery, yielding a representative cohort of US hospitalizations.

The Clinical Classifications Software codes 128, 197, 3, and 7 were used to identify a diagnosis of asthma, any skin infection, bacterial, and viral infections, respectively. International Classification of Diseases, Ninth Revision, Clinical Modification procedure codes were used to identify use of ventilation (overall, <96 or ≥96 hours) and physical therapy. Mortality risk and functional severity
were classified according to the All Patient Refined Diagnosis-Related Group coded in NIS based on software developed by the 3M Health Information Services (2008). The All Patient Refined Diagnosis-Related Group incorporates severity of illness subclasses and is used to relate the type of patients treated to the costs incurred by the hospital. Discharge status was assessed.

### Statistical analysis
All data analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Weighted prevalences (95% CI) of hospitalization with a primary International Classification of Diseases, Ninth Revision, Clinical Modification codes of AD and/or eczema among inpatients were determined. Hospital cost for inpatient care was calculated based on the total charge of hospitalization and the cost-to-charge ratio estimated by the Healthcare Cost and Utilization Project. All costs were adjusted for inflation to the year 2014 according to the Consumer Price Index (US Bureau of Labor Statistics, 2015). Summary statistics were generated for LOS, inflation-adjusted cost-of-care, including sum, geometric mean, and 95% CI for hospitalizations with a primary or no diagnosis of AD-E.

All statistical models employed SURVEY procedures, including discharge trend weights, sample strata accounting 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. These models allow for representative weighted estimates of frequency and prevalence of hospital discharges across the United States.

Complete case-analysis was performed. Missing data were encountered in 74,042 (0.1%) for age, 174,562 (0.3%) for sex, and 0 (0.0%) for hospital region. Post hoc correction for multiple dependent tests was performed by minimizing the false discovery rate (Benjamini and Hochberg, 1995). Two-sided corrected P-values are presented and considered significant if ≤0.05.

### CONFLICT OF INTEREST
The authors state no conflict of interest.

### ACKNOWLEDGMENTS
This publication was made possible with support from the Agency for Healthcare Research and Quality (AHRQ), grant number K12 HS023011, the Dermatology Foundation and American Medical Association Foundation.

### AUTHOR CONTRIBUTIONS
JIS 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. JIS contributed to the study concept and design. JIS, DYH, and SN acquired the data. SN, JIS, DYH, and JPT analyzed and interpreted the data. SN and JIS provided the draft of the manuscript. SN, JIS, DYH, and JPT critically revised the manuscript for important intellectual content: JIS, SN, and DYH did the statistical analysis. JIS obtained funding.

### SUPPLEMENTARY MATERIAL
Supplemental material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1016/j.jid.2017.02.975.

### REFERENCES


