Increasing Incidence, Cost, and Seasonality in Patients Hospitalized for Cellulitis

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Using data from the National Inpatient Sample, 1998–2013, we show that hospitalizations for cellulitis have approximately doubled. Costs increased by 118% to $3.74 billion annually. In addition, hospitalizations for cellulitis are highly seasonal, peaking in summer months: incidence during the peak month of July is 35% higher than in February.

Keywords. cellulitis; cost; hospitalization; seasonality; trend.

Cellulitis is a common infection. Clinical signs and symptoms include swelling, warmth, erythema, and discomfort of the affected area [1]. Cellulitis is often preceded by damage to the integrity of the skin, most commonly through trauma, inflammation, or from venous insufficiency [2, 3]. However, many patients with cellulitis do not recall any specific trauma because small disruptions to the skin may be sufficient as a predisposing risk factor. In fact, small breaks between the toes are common sites of skin disruptions leading to cellulitis [4, 5], and, accordingly, the lower extremities are frequently involved. Most cases of cellulitis are caused by Gram-positive organisms including β-hemolytic streptococci and Staphylococcus *aureus*. However, some specific cases of trauma (eg, bites) may be associated with different organisms [1].

Mild cases can be treated on an outpatient basis with oral antimicrobials, but more severe infections require intravenous (IV) antibiotics and hospitalizations. Hospitalization is often indicated for patients who have failed outpatient treatment or for patients with severe systemic symptoms. Patient-level risk

factors for cellulitis include diabetes, tinea pedis, venous insufficiency, lymphedema, prior surgery, or radiation therapy [1–3]. However, much less is known about any environmental risk factors that may influence disease occurrence other than direct exposure to salt water or fresh water [1]. However, a few reports have described a seasonal pattern of disease with cases increasing during summer months [6, 7].

The purpose of this investigation is (1) to describe the incidence of hospitalizations for cellulitis and to characterize the associated trend; (2) to investigate seasonal patterns in cellulitis incidence; and (3) to estimate the annual cost of hospitalizations in the United States attributable to cellulitis.

METHODS

Data were extracted from the Nationwide Inpatient Sample (NIS), the largest all-payer database of discharges in the United States. The database is maintained as part of the Healthcare Cost and Utilization Project (HCUP) by the Agency for Healthcare Research and Quality and consists of a 20% stratified sample of nonfederal acute-care hospitals. Studies of this type are deemed nonhuman subjects research by the University of Iowa Institutional Review Board.

We identified every adult hospitalization for which the primary diagnosis was cellulitis over the period January 1998 to November 2013. We used the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9) codes for case ascertainment. There are no ICD-9 codes dedicated exclusively to cellulitis. Thus, we used codes 681.XX (cellulitis and abscess of finger and toe) and 682.XX (other cellulitis and abscess). Henceforth, we refer to diagnoses linked to these codes collectively as cellulitis.

To estimate a monthly incidence series, we aggregated by year and month, and we applied discharge weights to account for yearly changes in the sampling design. The discharge weights before 2012 were corrected for the fact that the NIS was redesigned significantly in 2012. We similarly estimated a monthly incidence series for any-cause admissions, and we converted this series into weights that were subsequently applied to the cellulitis incidence series to control for differences in overall admissions per month. This adjusted cellulitis series is thus normalized by the number of monthly admissions.

The adjusted cellulitis series was modeled using a linear time trend and a collection of fixed effects (ie, indicator variables) that represent monthly mean deviations from the overall trend. The cyclic nature of the series was captured by the monthly fixed effects. An autoregressive structure of order one [AR(1)] was used to account for temporal correlation in the residuals. In the regression equation, the nadir month of February

is the baseline. Thus, the coefficient for the peak month of July is interpretable as the "average amplitude of seasonality" adjusted for the time trend. Similar analyses were performed on the log-transformed series, where the estimated changes in monthly incidence can be interpreted as percentages. All analyses were performed using R version 3.1.2 and SAS version 9.4.

We also separately analyzed subgroups based on region (North, South, East, West), gender (male, female), and age (18 to 35, 36 to 53, 54 to 72, and 72+). The autocorrelation structure for each subgroup's series was selected based on the Bayesian Information Criterion.

We used discharge weights provided by HCUP to produce national estimates of total and median cost as well as the median length of stay for all cellulitis discharges in our latest full year of data (2013). Because the listed "total charges" for each discharge is an overestimate of the actual cost of inpatient care, the value was adjusted using the cost-to-charge ratios estimated by HCUP. Because the earliest available cost-to-charge data is from 2001, this is the earliest comparison year for costs. Standard errors on the national estimates were calculated in accordance with the sampling design of the NIS.

RESULTS

In 1998, there were approximately 300 000 adult cellulitis hospitalizations nationally. In 2013, this number increased to approximately 537 000. Figure 1 displays this trend along with the one-step-ahead predictions from our model fit to the time series. We found that incidence was higher in the summer and lower in the winter; over the course of the study, the nadir month was February, and the peak was July. Adjusting for the trend, the average increase from February to July was 10 050.7 cases (95% confidence interval [CI], 9319–10 782). This equates to a percentage increase of 34.84% (95% CI, 31.9–37.9). Since 1998, incidence has been increasing by an average of 15 685.6 cases per year after adjusting for seasonality (95% CI, 14 134–17 237).

We found similar patterns of strong seasonality and increasing incidence across all age groups, genders, and regions. The
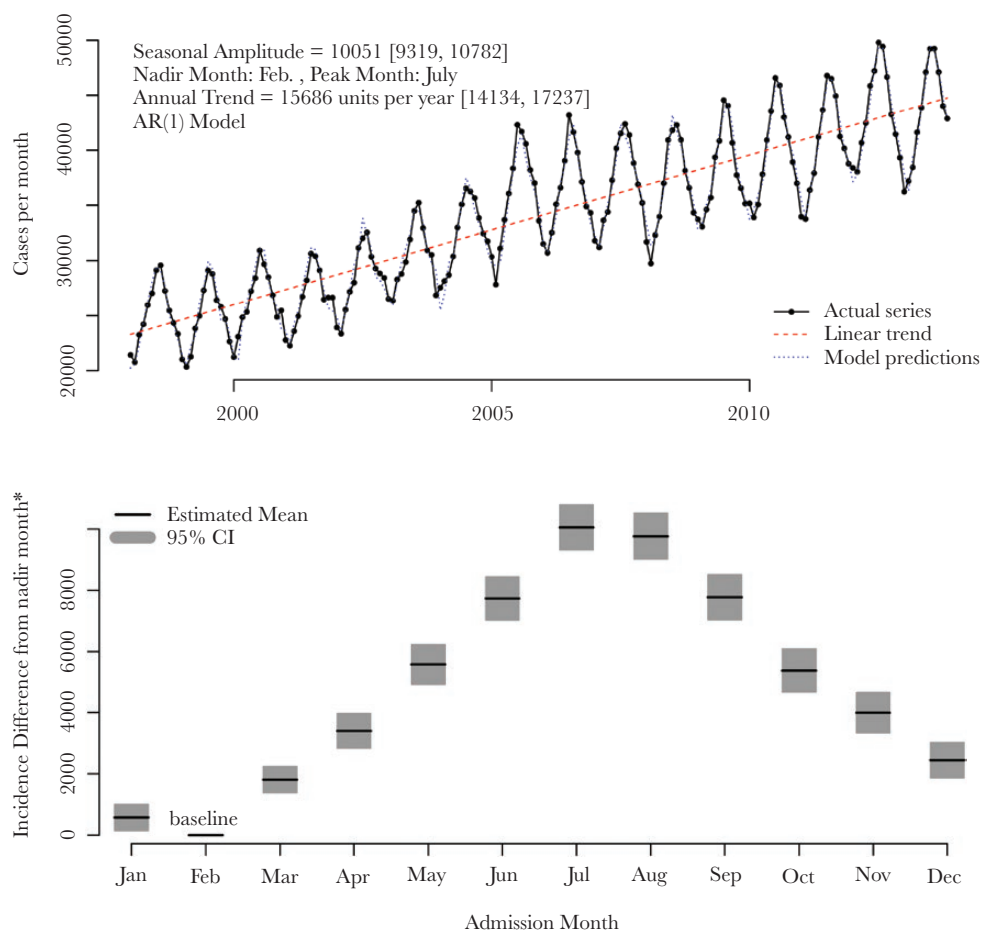

Figure 1. Monthly primary cellulitis hospitalizations in the United States normalized by overall admissions (top), and estimated mean differences between the number of admissions in the nadir month of February and all other months (bottom) (Nationwide Inpatient Sample, 1998–2013). Differences in means are estimated using an autoregressive structure of order one [AR(1)] model that controls for the yearly trend. *Differences in means are estimated using an AR(1) model on the *log-transformed* series that controls for the yearly trend.

incidence increased most among those ages 18–35 (5.63%; 95% CI, 4.0–7.3) and least among those ages 72 and over (2.86%; 95% CI, 2.7–3.0). Seasonality was strongest for those ages 54–71 (41.65%; 95% CI, 38.6–44.7) and weakest for those ages 18–35 (29.03%; 95% CI, 26.2–31.9). Seasonality was weakest in the western census region (23.79%; 95% CI, 21.0–26.7) and strongest in the southern census region (39.77%; 95% CI, 37.0–42.6). Although cellulitis incidence increased for men and women at the same rate, seasonality for men (39.48%; 95% CI, 37.3–41.7) was significantly greater than for women (31.41%; 95% CI, 29.4–33.4).

The total cost for all cellulitis discharges in 2013 was $3.74 billion (95% CI, $3.65 billion–$3.83 billion). The median cost per visit was $5159 (95% CI, $5103–$5215), and the median length of stay per visit was 2.88 days (95% CI, 2.86–2.90).

DISCUSSION

Our results show a striking increase in incidence in hospital admissions for cellulitis during our study period. Accordingly, the healthcare charges attributable to hospitalizations for cellulitis have more than doubled. In addition to increasing incidence, we observed a striking degree of seasonality with admissions for cellulitis consistently peaking in summer months and bottoming in winter months. Admissions for cellulitis are so seasonal that during the peak month of July, incidence is 34.8 percent higher than the baseline month of February during our study.

Our study period corresponded with a dramatic increase in skin and soft tissue infections caused by methicillin-resistant *S aureus* (MRSA) infections [8–10], although toward the end of our study period, some report a decrease in MRSA infections [11]. Thus, the change in incidence we report could be at least partly a function of the increase in incidence of MRSA infections, especially because outpatient treatment options for MRSA are more limited than those for other common pathogens that cause skin infections. Alternatively, there may be an increase in the severity of such infections. Regardless of the cause, the increase in admissions for cellulitis resulted in a substantial increase in healthcare costs; in 2013, adult hospitalizations for a primary diagnosis of cellulitis resulted in almost $4 billion. Thus, even shifting a small proportion of admissions to outpatient care represents a worthwhile target for not only lowering cost, but also sparing patients from hospital admissions. These results indicate the importance of outpatient therapies for cellulitis. Given that the median cost for an adult cellulitis admission in 2013 was over $5000 with a median length of stay of 2.88 days, another priority should be to develop approaches to help discharge patients sooner, either on IV therapy or with oral medications, or develop ways to treat while avoiding admissions. Indeed, if annual admissions for cellulitis were reduced by a modest 5%, the resulting savings could be almost $200 million annually.

Many infectious diseases display seasonal patterns [12]. Among respiratory infections, influenza and respiratory syncytial virus are highly seasonal with peaks during winter months. In contrast, in the Northern Hemisphere, tick-borne infections such as Lyme disease and ehrlichiosis as well as mosquito-borne infections peak in summer months. Gram-negative bloodstream infections [13, 14] and surgical site infections also increase during the summer months [15–17]. However, much less attention has been focused on the seasonality of skin and soft tissue infections than other diseases described as seasonal. Although some prior reports have mentioned the seasonality of skin and soft tissue infections [18, 19], seasonality has not been the primary focus of studies of risk factors for cellulitis. However, our results show a clear pattern of seasonality; although cases continue to occur in winter months, the gap between peak and nadir months is substantial.

The reason that cellulitis incidence exhibits a seasonal pattern is unclear. Other seasonal diseases are thought to be partly affected by weather, seasonal travel or gatherings or the indirect effects of weather on disease vectors [12]. One report from France demonstrated an association between increased temperatures and hospital admissions for cellulitis [20]. Future investigations should focus on the direct effects of weather on the epidemiology of cellulitis. Such investigations may help lead to a better understanding of cellulitis' pathogenesis and risk factors. In addition, more knowledge regarding environmental risk factors may lead to new preventive approaches or at least methods that can better anticipate an increase in cellulitis incidence as early treatment may improve outcomes.

Our study's data source has some inherent limitations. First, because we exclusively use administrative data and do not have medication or laboratory data, we cannot directly incorporate information regarding microbiology or antimicrobial drug resistance into our analysis. In addition, we used ICD-9 codes to identify cases. Cellulitis is sometimes difficult to diagnose and can be confused with other noninfectious syndromes that can cause redness and swelling (eg, venous stasis). In addition, there are no ICD-9 codes referring to only cellulitis, other forms of soft tissue infections may be included in our series (ie, skin abscesses), and this could influence our findings. Second, our data source does not include pharmacy data detailing treatment approaches. Third, we only observe events from inpatient admissions and do not observe outpatient cellulitis incidence, yet cellulitis is often treated on an outpatient basis. Only severe cases of cellulitis are admitted to a hospital. Thus, our data source biases our analysis by including only the more severe cases. Fourth, our data do not allow us to uniformly infer the extent and severity of the cellulitis. Finally, because our data source does not include patient identifiers, we are unable to determine whether patients have been readmitted which is likely to occur for severe cases of cellulitis.

CONCLUSIONS

Despite our limitations, we demonstrate the dramatic increase in cases requiring hospitalization and the increase in cost from hospitalized care for cellulitis. Both of these findings stress the importance of new approaches to prevent or reduce hospitalizations for cellulitis treatment. In addition, we show the striking seasonality of hospitalizations for cellulitis and highlight the need for future work describing how and why admissions for cellulitis are seasonal.

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