The Burden of Staphylococcus aureus Infections on Hospitals in the United States

An Analysis of the 2000 and 2001 Nationwide Inpatient Sample Database

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Background: Previous studies have investigated the impact of Staphylococcus aureus infections on individual hospitals, but to date, no study using nationally representative data has estimated this burden.

Methods: This is a retrospective analysis of the 2000 and 2001 editions of the Agency for Healthcare Research and Quality’s Nationwide Inpatient Sample database, which represents a stratified 20% sample of hospitals in the United States. All inpatient discharge data from 994 hospitals in 28 states during 2000 and from 986 hospitals in 33 states during 2001, representing approximately 14 million inpatient stays, were analyzed to determine the association of S aureus infections with length of stay, total charges, and in-hospital mortality.

Results: Staphylococcus aureus infection was reported as a discharge diagnosis for 0.8% of all hospital inpatients, or 292,045 stays per year. Inpatients with S aureus infection had, on average, 3 times the length of hospital stay (14.3 vs 4.5 days; P<.001), 3 times the total charges ($48,824 vs $14,141; P<.001), and 5 times the risk of in-hospital death (11.2% vs 2.3%; P<.001) than inpatients without this infection. Even when controlling for hospital fixed effects and for patient differences in diagnosis-related groups, age, sex, race, and comorbidities, the differences in mean length of stay, total charges, and mortality were significantly higher for hospitalizations associated with S aureus.

Conclusions: Staphylococcus aureus infections represent a considerable burden to US hospitals, particularly among high-risk patient populations. The potential benefits to hospitals in terms of reduced use of resources and costs as well as improved outcomes from preventing S aureus infections are significant.

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STAPHYLOCOCCUS AUREUS IS A frequent cause of healthcare-associated infections in acute care hospitals. It is the most common cause of nosocomial pneumonia and surgical site infections and the second most common cause of bloodstream, cardiovascular, and eye, ear, nose, and throat infections. An increasing percentage of S aureus infections are caused by antimicrobial-resistant strains of the organism, with some medical centers reporting that more than half of S aureus isolates are methicillin resistant. Knowledge of the impact of S aureus infections on a national level is helpful for medical personnel, hospital administrators, and payers who make financial and policy decisions to prevent the spread of this organism.

To date, no study using nationally representative data has estimated the impact of S aureus infections in terms of clinical and financial outcomes such as length of stay (LOS), total charges, and in-hospital mortality. Rubin and colleagues estimated the death rate, infection rate, and direct medical costs related to S aureus infections for all hospitalized patients in New York City in 1995. Other studies have considered the additional costs and hospital days associated with surgical site infections and other types of hospital infections for all inpatients or for specialized groups of patients, including patients who undergo orthopedic surgery or coronary artery bypass grafting procedures. Recently, McGarry and colleagues considered the clinical and financial outcomes associated with S aureus infections, but this study compared elderly patients with S aureus infections with elderly patients without S aureus infections and with nonelderly patients with S aureus infections. The scope of each of these studies was limited to a maximum of a few hospitals for specific cohorts of patients, and not all of these studies were specific to S aureus.

The objective of this study is to provide a national estimate of the burden of...
S aureus infections on US hospitals through analysis of a nationally representative database. The main outcome measures are LOS, total charges, and in-hospital mortality rates.

**METHODS**

**DATA AND VARIABLES**

The 2000 and 2001 Nationwide Inpatient Sample (NIS), developed by the Agency for Healthcare Research and Quality, was the primary data source for this analysis. The NIS is the largest all-payer inpatient care administrative database in the United States. Each year of the NIS contains discharge data on approximately 7 million hospital inpatient stays.12 By design, the NIS approximates a stratified 20% sample of US hospitals, which the American Hospital Association defines as “all nonfederal, short-term, general, and other specialty hospitals, excluding hospital units of institutions.”13 Public hospitals and academic medical centers are included, as are specialty hospitals. Long-term care hospitals, psychiatric hospitals, and alcoholism/chemical-dependency treatment facilities are not included. All discharge data were captured for 986 hospitals in 33 states by NIS 2001 and for 994 hospitals in 28 states by NIS 2000. We used 2 years of NIS data for the analysis to increase the sample size and, therefore, to increase the external validity of the analysis.

We analyzed patient hospital stays in terms of 7 strata: (1) all inpatients; (2) all inpatients who underwent a surgical procedure; (3) all inpatients who underwent an invasive procedure—(4) cardiovascular, (5) orthopedic, or (6) neurosurgical (analyzed together and separately); and (7) burn unit inpatients. We identified clinically similar operative procedures according to the methods described by the National Nosocomial Infections Surveillance system of the Centers for Disease Control and Prevention.3

**EXPERT PANEL**

A 4-member expert panel (G.A.N., R.J.R., J.J.S., and J.K.) validated the approach by providing guidance on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding interpretation, identifying high-risk inpatients to analyze and identifying the comorbidities for which to control. The expert panel included an infectious disease specialist involved in hospital epidemiology, a nephrologist with significant health services research and health policy experience, a doctor of pharmacy with extensive research experience with antimicrobials, and a research physician involved in numerous S aureus and hospital infection studies.

**IDENTIFYING INFECTIONS**

We identified S aureus infections by using ICD-9-CM discharge diagnosis codes14; we used these rather than admission diagnosis because discharge diagnosis is considered to more accurately reflect the patient’s actual diagnosis.15 We considered a hospital stay to be S aureus–related if the NIS record had either (1) an S aureus–specific infection code or (2) the S aureus microorganism code (041.11) in conjunction with an infections possibly due to S aureus (Table 1). Included codes were validated by the expert clinical panel. Hospital stays related to multiple S aureus infections were counted only once in the calculation of the S aureus infection rate. Because hospitals have no financial incentives to code S aureus–specific codes, unlike the financial incentives that exist for coding infection-specific codes, it is likely that the intersection of microorganism codes and infection codes represent a lower-bound estimate of the prevalence of S aureus–related infections. In our analysis we did not distinguish between principal or secondary diagnoses of S aureus infections. For the purposes of our analysis, infections that occurred before admission to the hospital or during a hospital stay are treated identically.

In our analysis, we defined related to invasive surgical procedures according to the National Nosocomial Infection Surveillance system, which has established criteria for operative procedures.1 We reviewed the system’s ICD-9-CM procedure codes and grouped them into 1 or more of the 7 types of hospital stays.

**ANALYTICAL APPROACH**

We performed statistical analyses to compare the characteristics of hospital inpatients with S aureus infections with all other hospital inpatients and with inpatients with other types (non–S aureus) of infections. For each analysis, we calculated descriptive statistics as well as tests for statistical significance.

We performed several analyses to estimate the marginal effect of an S aureus infection on expected LOS, expected total charges for the stay, and in-hospital, same-stay mortality rate. To more accurately attribute LOS, charges, and mortality to S aureus infection in the administrative NIS data, adequate control of confounding is necessary. We therefore performed multivariable regression analysis16 using the computer software programs PROC SURVEYREG17 (SAS Inc, Cary, NC) (for LOS and charges) and PROC SURVEYLOGISTIC (SAS) (for mortality), controlling for hospital fixed effects and patient variables such as diagnosis-related group, age, sex, race, and payer, as well as certain comorbidities (diabetes, lung disease, and dialysis) identified by the expert panel.

As a confirmatory analysis, we performed multivariable matching to compare cases of S aureus infection with controls that share similar characteristics. The matching analysis provides a cross-validation of our regression analysis in light of the limitations of large administrative data sets.18 For all inpatients, each identified S aureus infection case was matched with 1 control from the same hospital and with the same age, sex, and race. Cases with a certain comorbidity (diabetes, lung disease, and dialysis) were matched with controls with 1 or more of these comorbidities. The matching algorithm first selected controls who met the matching criteria and then randomly selected only 1 control if multiple eligible matching controls were found. This same matching algorithm was also applied to each...
of the other inpatient types. Each inpatient type with an *S. aureus* infection had at least 1 matching control. To be consistent, we applied a 1-on-1 matching algorithm to each stay type. Excess LOS was defined as the difference in LOS between a case and a matching control. Similar analyses were performed for excess charges and excess mortality.

We present results as an annual average. We converted hospital charges in 2000 to 2001 charges via the Consumer Price Index for Medical Care, Hospital, and Related Services** and expressed total charges in year 2001 dollars. Note that charges are not the same as the cost of a patient stay; they include hospital overhead costs, charity care, and bad debt, among other costs. *P* values of less than .05 were considered statistically significant.

### RESULTS

*Staphylococcus aureus* infection was reported as a discharge diagnosis for 0.8% of all hospital inpatients, or an average of 292 045 inpatients a year (Table 2). Among the stay types analyzed, *S. aureus* infections were most likely to occur in inpatients who had undergone invasive neurosurgery (1.4%) and least likely to occur in inpatients who had undergone orthopedic surgery (0.3%).

Patients with *S. aureus* infections were more likely to be older (mean age, 63.4 vs 47.3 years; *P* < .001) and male (53.2% vs 40.7%; *P* < .001) than other patients (Table 3). In addition, patients with *S. aureus* infections were more likely to have Medicare as their primary payer (61.7% vs 36.5%; *P* < .001), which correlates with the older average age of patients with *S. aureus* infections. A higher percentage of patients with *S. aureus* infections had diabetes, lung disease, or had undergone dialysis compared with patients not infected with this organism.

Table 2 compares the average LOS, charges, and in-hospital mortality rates of inpatients with *S. aureus* infections vs all other inpatients. Inpatients with *S. aureus* infections had longer average LOS, higher total charges, and higher in-hospital mortality rates than other inpatients. The average LOS for inpatients with *S. aureus* infections was 3 times longer than that of other inpatients (14.3 vs 4.5 days; *P* < .001). The total hospital charges for inpatients with *S. aureus* infections were more than 3 times the total charges for other inpatients ($48 824 vs $14 141; *P* < .001). In both LOS and total charges, the differential was greatest for burn unit inpatients (32.6 vs 7.3 days, *P* < .001; $203 363 vs $28 871; *P* < .001). Inpatients with *S. aureus* infections had higher total charges than other inpatients ($48 824 vs $14 141; *P* < .001).
infections had a nearly 5-fold risk of in-hospital death compared with other inpatients (11.2% vs 2.3%; P<.001). The differential in absolute risk of mortality was greatest for inpatients who had undergone invasive cardiovascular procedures (14.3% vs 3.1%; P<.001).

Even when controlling for hospital fixed effects and for patient differences in age, sex, race, payer, diagnosis-related groups, and comorbidities, the mean LOS, total charges, and mortality were considerably higher for \textit{S. aureus}–infected patients. Table 4 displays the results of the multivariable linear and logistic regression analyses using the PROC SURVEYREG and PROC SURVEYLOGISTIC commands, respectively. The impact of \textit{S. aureus} on differences in LOS and total charges was greatest for burn unit inpatients (+23.8 days; +$161,343). The difference in absolute risk of in-hospital death was greatest for inpatients who had undergone invasive orthopedic procedures (+8.1%).

To account for the fact that LOS and total charges are not usually normally distributed, we also conducted regression analyses of the log transformations of LOS and of total charges on the covariates mentioned herein. Although there were differences in the significance of some variables in the model, for all patient subgroup analyses, an \textit{S. aureus} infection was always significantly correlated with longer LOS and greater total charges (Table 4.)

Infections, regardless of type, occurred in approximately 22.5% of all inpatients. Infections were most common among burn unit inpatients (24.0%) and least common among inpatients who had undergone invasive orthopedic surgery (8.4%). When compared with patients with other types of infections, differences in outcomes of patients with \textit{S. aureus} infections persisted. Table 4 shows that inpatients with \textit{S. aureus} infections had significantly longer average LOS, greater total charges, and higher in-hospital mortality rates than inpatients with other types of infections. The multivariable and logistic regression analysis estimates of the excess LOS, charges, and mortality appear in Table 4.

Results of multivariable matching analyses for each inpatient stay type corroborated with the results of the regression analyses (Table 5). For all inpatients with \textit{S. aureus} infections, the average LOS was 9.2 days longer and $36,119 more expensive than for inpatients without \textit{S. aureus} infections. Again, the differences in LOS and total charges were greatest for burn unit inpatients (20.3 days and $157,268), followed by all inpatients who had undergone invasive neurosurgery (18.7 days and $80,470). The difference in absolute risk of in-hospital death was greatest for inpatients who had undergone invasive cardiovascular procedure (+6.1%).

<table>
<thead>
<tr>
<th>Type of Case</th>
<th>Compared With Inpatients Without \textit{S. aureus}</th>
<th>Compared With Inpatients With Other Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Impact on LOS, d*</td>
<td>Impact on Charges, $†</td>
</tr>
<tr>
<td>All inpatients</td>
<td>+9.1</td>
<td>+32,856</td>
</tr>
<tr>
<td>Inpatients who had undergone invasive surgery</td>
<td>+13.6</td>
<td>+49,215</td>
</tr>
<tr>
<td>Inpatients who had undergone invasive orthopedic, cardiovascular, and neurosurgical procedures</td>
<td>+16.8</td>
<td>+68,944</td>
</tr>
<tr>
<td>Inpatients who had undergone invasive cardiovascular surgery</td>
<td>+16.4</td>
<td>+67,499</td>
</tr>
<tr>
<td>Inpatients who had undergone invasive orthopedic surgery</td>
<td>+14.6</td>
<td>+56,134</td>
</tr>
<tr>
<td>Inpatients who had undergone invasive neurosurgical procedures</td>
<td>+16.9</td>
<td>+76,858</td>
</tr>
<tr>
<td>Burn unit inpatients</td>
<td>+23.8</td>
<td>+161,343</td>
</tr>
</tbody>
</table>

Table 4. Impact of \textit{Staphylococcus aureus} Infections on Length of Stay, Charges, and In-Hospital Mortality

Abbreviation: LOS, length of stay.

* P values reflect the significance of the impact of \textit{S. aureus} on the length of stay after LOS was log-transformed. P<.001 for all. Impact on LOS and charges estimated via multivariable linear regression using PROC SURVEYREG (SAS Inc, Cary, NC) controlling for hospital fixed effects and patient variables diagnosis-related group, age, sex, race, payer, diabetes, dialysis, and lung disease.

†P values reflect the significance of the impact of \textit{S. aureus} on total charges after total charges were log-transformed. P<.001 for all.

‡Impact on absolute risk of in-hospital mortality estimated via multivariable linear regression using PROC SURVEYLOGISTIC (SAS Inc), controlling for patient variables age, sex, race, payer, diabetes, dialysis, lung disease. Hospital charges do not include physician professional fees.

The results of this analysis are consistent with the limited number of analyses that have already reported the prevalence of \textit{S. aureus} infections. Rubin and colleagues estimated that 1.0% of all nonobstetrical hospital discharges in New York City were patients with \textit{S. aureus} infections. After removal of obstetrical inpatients from our analysis, the prevalence rate of \textit{S. aureus} infection inpatients was 0.91%. Although the infection rate observed by Perl and colleagues was higher than the rate we calculated, their study was a clinical trial with 447 closely observed surgical patients, whereas our study analyzed an administrative database at the stay level that is likely to provide an underestimate of the true prevalence of \textit{S. aureus} due to undercoding of the microorganism.

The observation that patients with \textit{S. aureus} infections have worse clinical and financial outcomes than patients who do not have \textit{S. aureus} infections is similar to...
the findings of the limited number of previous studies, which have largely focused on specific populations or individual hospitals. Rubin and colleagues found that inpatients with S aureus infections had more than twice the LOS (20 vs 9 days), more than twice the direct medical costs ($32 100 vs $13 263), and more than twice the death rate (10% vs 4%) of other inpatients. Results of sensitivity analyses dropping obstetrical stays in our analysis had no impact on our regression results for LOS, total charges, and mortality. Recently, in an investigation of the impact of S aureus on the elderly, McGarry and coworkers demonstrated that elderly patients with S aureus were at increased risk for mortality (odds ratio 5.4), postoperative hospital days (2.5-fold increase), and hospital charges (2.0-fold increase) compared with elderly patients without S aureus infections.

Our study found that approximately 292 045 US hospital inpatients in a given year have S aureus infections. After controlling for confounders, the marginal impact of S aureus infections on a stay level is estimated to be 9.1 days in excess LOS, $32 856 in excess charges, and 4.0% in excess in-hospital mortality. Applying these per hospital–stay estimates to the total number of inpatients with S aureus in the United States in a given year results in an estimated 2.7 million days in excess LOS, $9.5 billion in excess charges, and close to 12,000 inpatient deaths per year.

Our analysis has several limitations. First, the sensitivity and specificity of our identification of inpatients with S aureus infections depend on the completeness and accuracy of the ICD-9-CM coding in the NIS administrative database. The ICD-9-CM coding system was not designed to track infection prevalence and therefore was not clinically precise in our study. Coding practices may vary across hospitals, and financial incentives for hospitals may influence the accuracy of coding. Moreover, the diagnosis coding in the database does not allow for reliable differentiation between methicillin-resistant and methicillin-susceptible S aureus, which might have an impact on costs and outcome. The inability to isolate methicillin-resistant S aureus infections is a notable limitation to our analysis. In a recent study, Kaye and colleagues demonstrated how the choice of reference group affected the outcomes of hospital days after surgery, total charges, and mortality when comparing methicillin-resistant S aureus, methicillin-susceptible S aureus, and uninfected control group patients.

Second, because the NIS does not provide information on the sequence of events during a patient’s hospital stay, it is not possible to determine whether a patient had S aureus colonization or infection before entering the hospital or at what point during a hospital stay the patient developed an S aureus infection. As such, it is not possible to determine whether an S aureus infection was community acquired or health care associated, and even if it was hospital acquired, it is not possible to identify and control for at-risk time preceding infection. Nevertheless, in the subgroups of patients who underwent cardiovascular surgery, orthopedic surgery, and neurosurgery, most of the infections caused by S aureus were most likely nosocomial.

Third, because each record in the NIS is limited to the duration of a hospital stay, it does not provide patient-level information regarding hospital readmission, transfer, or mortality due to S aureus complications following discharge. Therefore, the in-hospital, same-stay mortality rate provides only limited information on the crude mortality rate of patients with S aureus infections. In a single hospital study of patients who developed surgical site infections after undergoing coronary artery bypass grafting, infection occurred an average of 21.5 days after the procedure, and most cases were diagnosed on readmission (59%) or postdischarge surveillance (16%). In addition, terminally ill patients may move from hospitals to hospice or palliative care facilities for their final weeks of life. A 30-day or 6-month mortality rate is likely a better measurement of the true mortality rate due to S aureus infections. Our inability to measure “out-of-hospital” mortality, or death subsequent to the hospital stay, likely underestimates the impact of S aureus infections on mortality.

Despite these limitations, this study leveraged the large number of records in the NIS data sets and allowed for the derivation of estimates while controlling for potential confounding variables (including patient demographics, comorbid conditions, hospital, and payer). The simi-

Table 5. Confirmatory Analysis: Results of Multivariable Matching

<table>
<thead>
<tr>
<th>Type of Case</th>
<th>1:1 Match Rate, %†</th>
<th>Excess LOS, d</th>
<th>Excess Charges, $‡</th>
<th>Excess Absolute Risk of In-Hospital Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All inpatients</td>
<td>100</td>
<td>+9.2</td>
<td>+36 119</td>
<td>+3.4</td>
</tr>
<tr>
<td>Inpatients who had undergone invasive surgery</td>
<td>100</td>
<td>+11.3</td>
<td>+48 569</td>
<td>+3.1</td>
</tr>
<tr>
<td>Inpatients who had undergone invasive orthopedic, cardiovascular, and neurosurgical procedures</td>
<td>100</td>
<td>+16.7</td>
<td>+65 477</td>
<td>+5.2</td>
</tr>
<tr>
<td>Inpatients who had undergone invasive cardiovascular surgery</td>
<td>100</td>
<td>+17.9</td>
<td>+73 443</td>
<td>+6.1</td>
</tr>
<tr>
<td>Inpatients who had undergone invasive orthopedic surgery</td>
<td>100</td>
<td>+14.2</td>
<td>+51 866</td>
<td>+2.4</td>
</tr>
<tr>
<td>Inpatients who had undergone invasive neurosurgical procedures</td>
<td>100</td>
<td>+18.7</td>
<td>+80 470</td>
<td>+5.8</td>
</tr>
<tr>
<td>Burn unit inpatients</td>
<td>100</td>
<td>+20.3</td>
<td>+157 268</td>
<td>+0.0</td>
</tr>
</tbody>
</table>

*P<.001 for all comparisons except burn unit patients and excess charges (P = .002) and excess absolute risk of in-hospital mortality (P > .99).
†Percentage of cases (ie, Staphylococcus aureus stays) with at least 1 matched control (ie, non–S aureus stay) based on hospital, sex, age, and race. Excess length of stay (LOS) is the difference in LOS for a case minus a matching control. The 1-sample t test was used to test the hypothesis that the mean excess LOS is significantly different from 0. Excess charges and their significance were calculated similarly. The significance of the excess mortality rate was calculated using the Wilcoxon signed-rank test.
‡Does not include physician professional fees. Percentage of cases with at least 1 matching control.
larity in results derived from matching and from regression analysis serve to validate the findings.

The impact of *S aureus* on patients and hospitals may be partially ameliorated by attempts to reduce the microbial burden or reduce nosocomial transmission. Strategies to reduce the burden of *S aureus* infections are available to hospitals. Laboratory culture techniques, as well as newer techniques that use polymerase chain reaction, can be used to screen patients for *S aureus* nasal carriage. Previous studies in the United States, Europe, and Japan have found evidence that eliminating *S aureus* carriage in the nares using mupirocin nasal ointment may reduce *S aureus* surgical site and/or nosocomial infections. Other techniques for eliminating nasal carriage of *S aureus* include the administration of systemic antibiotics, which has had disappointing results, and the active colonization of patients with the 502A strain of *S aureus*, which can prevent colonization by more virulent types of the organism but can still cause serious complications. Hospitals could use preadmission screening for *S aureus* and decolonizing *S aureus*–positive patients to avoid some of the considerable increases in LOS, total charges, and mortality associated with *S aureus* infections.1,11,24,28,31

In summary, *S aureus* infections present a considerable cost burden to US hospitals. Almost 1% of all US hospital stays involve an *S aureus* infection. On a national level, the burden of *S aureus* infections is staggering: almost 12,000 inpatient deaths annually and an estimated 2.7 million days in excess LOS and $9.5 billion in excess charges. Not all of the differences in clinical and economic outcomes can be attributed to the presence of the *S aureus* infection. However, when hospital stays of inpatients with *S aureus* infections are compared with those of inpatients with other infections, *S aureus* is still associated with significantly higher mortality and total charges and longer LOS.

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