Editorial

Is the Burden of *Staphylococcus aureus* Among Patients With Surgical-Site Infections Growing?

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Surgical-site infections (SSIs) are an important cause of illness and death among individuals receiving healthcare.[1] *Staphylococcus aureus* has consistently been reported as the most frequent cause of infections at surgical sites, and, because it is more virulent than other frequent causes, accounts for a large proportion of the morbidity and mortality associated with these infections.[2,3] In this issue of *Infection Control and Hospital Epidemiology*, a series of articles address various issues regarding SSIs and their etiology.[4-8] A consistent theme among these articles is the gravity and frequency of *S. aureus* as a cause of infections in surgical patients, and the findings suggest that the proportion and clinical impact of SSIs caused by *S. aureus* may be increasing.

In the first article addressing this subject, McGarry et al.[4] examine the impact of *S. aureus* SSI on clinical and fiscal outcomes among elderly patients. In this nested cohort study, elderly patients (70 years or older) with *S. aureus* SSI were compared with elderly surgical patients who did not develop infection, as well as with a group of younger patients (18 to 60 years old) with SSI due to *S. aureus*. When compared with uninfected patients of similar age and with similar underlying illnesses, elderly patients with *S. aureus* SSI had a higher mortality rate, longer hospitalization, and increased hospital charges. In addition, when older patients were compared with younger patients with *S. aureus* SSI in multivariate analyses controlling for comorbid illnesses, procedure type, and other factors, the investigators found that being 70 years of age or older was an independent predictor of death (adjusted odds ratio, 2.9; 95% confidence interval, 1.1 to 7.6), longer hospital stay (13 vs 9 days; $P = .001$), and increased hospital charges ($45,767 vs $85,648; $P < .001$). These data suggest that the clinical impact of *S. aureus* SSI may be more severe among elderly patients when compared with younger patients who have similar infections. Although these findings may not be unexpected, they do carry particular significance considering the changing demographic of the U.S. population. Increasing life expectancy and the aging of the "baby boomer" generation are expected to contribute to a dramatic increase in the number of older individuals living in this country during the next two decades. U.S. Census Bureau projections forecast that between 2000 and 2020 there will be a 56% increase in the number of individuals 65 years of age and older.[9] As a result, larger numbers of elderly patients will require surgery in the coming years. In one projection, cardiothoracic and orthopedic surgical work is expected to grow by 42% and 28%, respectively, between 2001 and 2020.[10] If *S. aureus* SSI rates remain constant, then the number of *S. aureus* SSIs among the elderly, a particularly vulnerable group as suggested by the article from McGarry et al.,[4] will increase substantially.

Three additional articles published in this issue of *Infection Control and Hospital Epidemiology*[5-7] suggest that *S. aureus* may be playing an increasingly prominent etiologic role in SSI associated with coronary artery bypass graft (CABG) procedures and joint replacement surgery, procedures that are performed primarily in elderly patient populations. In a review of 3,443 CABG procedures performed in a Detroit hospital, Sharma et al.[5] report that sternal SSI developed in 122 (3.5%). *S. aureus* was the most frequently isolated pathogen, accounting for 46 (49%) of the SSIs in which a single pathogen was isolated. Of the 55 infections caused by *S. aureus*, 20 (36%) were caused by

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methicillin-resistant *S. aureus* (MRSA). These investigators also noted that secondary bacteremia occurred in 22 (18%) of the patients with SSI, and all of these cases were due to *S. aureus*; 7 (31.8%) were methicillin resistant. The authors also state that older age was significantly associated with deep SSIs. Similarly, in a series of 4,474 patients undergoing CABG procedures in five Australian hospitals,[6] SSI occurred in 346 (7.8%). Of the 296 infections for which an organism was isolated, *S. aureus* was found in 56%; of these isolates, 57% were methicillin resistant.

Prospective surveillance by Minnema et al.[7] identified 22 cases of SSI following total knee replacement surgery in a Toronto hospital during a 3-year period. Of the 19 infections for which an etiologic organism was identified, *S. aureus* was present in 10 (52.6%). The authors performed a case–control study to identify risk factors associated with infection. On multivariate analyses, only two factors were independently associated with development of an SSI: the use of closed suction drainage and an increased postoperative international normalized ratio.

These case series of SSI following CABG procedures and total knee replacement are similar in the strikingly large proportion of infections caused by *S. aureus* (49% to 56%). Equally impressive is the prominence of MRSA as an etiologic agent among these infections. Preliminary analysis of data reported to the National Nosocomial Infections Surveillance (NNIS) System suggests that the experiences reported in this issue of *Infection Control and Hospital Epidemiology* may not be uncommon. Data from NNIS System hospitals reported between 1992 and 2002 show that among SSIs following CABG, cholecystectomy, colectomy, and total hip replacement, the overall proportion caused by *S. aureus* increased from 16.6% to 30.9%; the proportion of *S. aureus* infections attributable to MRSA increased from 9.2% to 49.3% (Centers for Disease Control and Prevention, NNIS System, unpublished data, May 5, 2004).

These data, showing that a large proportion of SSIs are apparently caused by *S. aureus*, suggest that prevention strategies successfully targeting *S. aureus* SSI could have a major impact on overall SSI rates and on the overall morbidity and mortality associated with SSIs. Numerous studies have shown that surgical patients who carry *S. aureus* in their anterior nares are at increased risk for *S. aureus* SSI, and that those infections are usually caused by the same strains that were carried by these patients prior to surgery.[11] These observations have led several investigators to examine the role of preoperative eradication of nasal *S. aureus* colonization in preventing *S. aureus* SSI. Following promising results from studies showing that SSI rates among patients who received preoperative intranasal mupirocin treatment were significantly lower than rates among historical controls,[12-14] two recent randomized, double-blind, placebo-controlled trials have examined the impact of preoperative mupirocin treatment on postoperative infection rates. In the trial conducted by Perl et al.,[15] there was no significant difference in the SSI rate between the mupirocin group and the untreated controls. However, in a subset analysis examining only those who harbored *S. aureus* in their nares, the rate of all nosocomial *S. aureus* infections (surgical and nonsurgical) following surgery was reduced by half among patients receiving mupirocin, and this reduction was statistically significant (odds ratio for infection, 0.49; 95% confidence interval, 0.25 to 0.92). *S. aureus* SSIs were reduced by 37% among the treated carriers, but this difference was not statistically significant. In a second double-blind, placebo-controlled trial, patients undergoing orthopedic surgery were randomized to preoperative treatment with intranasal mupirocin therapy.[16] Patients treated with mupirocin had fewer *S. aureus* SSIs (relative risk, 0.59; 95% confidence interval, 0.20 to 1.79) and fewer *S. aureus* SSIs caused by an endogenous strain (relative risk, 0.19; 95% confidence interval, 0.02 to 1.62), although these differences were not statistically significant. Due in part to smaller than expected infection rates in the placebo groups in both studies, neither had sufficient statistical power to conclude with confidence that the use of mupirocin was ineffective for prevention of *S. aureus* SSI.[16,17] The authors of both studies concluded that additional randomized, controlled trials should be performed to better determine whether selected populations of surgical patients might benefit from preoperative eradication of *S. aureus* colonization.

On the basis of the available evidence, some centers have adopted the use of prophylactic intranasal mupirocin to prevent subsequent *S. aureus* infections among certain surgical patients.[18] Due to concerns about the emergence of mupirocin resistance and the fact that treating all surgical patients would result in unnecessary antimicrobial exposure for many, there has been interest in using a focused strategy in which only those known to be *S. aureus* carriers are treated.[19,20] This strategy requires correct identification of *S. aureus* carriers prior to surgery. Another article in this issue of *Infection Control and Hospital Epidemiology* provides information of relevance to such identification strategies. Herwaldt et al.[8] examined factors associated with *S. aureus* colonization among the same 4,030 patients enrolled in one of the previously mentioned clinical trials.[15] During that trial, data on 70 patient characteristics that might be associated with *S. aureus* carriage were collected at the time of enrollment. Nasal colonization with *S. aureus* was detected in 891 (22%) of the patients, and on multivariate analyses, only obesity, male gender, and a history of a cerebrovascular accident were found to be independent risk factors for carriage. The authors conclude that it will be difficult for surgeons to use clinical and epidemiologic information to develop algorithms that predict accurately which patients carry *S. aureus* in their nares, and thus laboratory tests must be used. They argue that results of preoperative cultures are too slow to be of practical use in many surgical settings, and therefore rapid methods of identifying carriage may be the best method to guide surgeons who choose to eradicate *S. aureus* nasal colonization in their patients prior to surgery.[19]

Another striking feature of the articles in this issue of *Infection Control and Hospital Epidemiology* and in the pre-

liminary analysis of NNIS System data is the apparent rise in the proportion of SSIs caused by MRSA. This trend may have important implications for the overall clinical impact of SSI caused by *S. aureus*. A recently published study examined the impact of methicillin resistance on the outcomes of 286 patients with *S. aureus* SSI. Engemann et al.[21] found that 25 (20.7%) of 121 patients with MRSA SSI died during the 90-day postoperative period, compared with 11 (6.7%) of 165 patients with SSI caused by methicillin-susceptible *S. aureus* (MSSA) (odds ratio, 3.6; 95% confidence interval, 1.7 to 7.4; $P < .001$). On multivariate analyses, methicillin resistance remained independently associated with both increased mortality as well as increased hospital charges among patients with *S. aureus* SSI. These results are similar to those of a recently published meta-analysis of *S. aureus* bacteremia studies suggesting that methicillin resistance was associated with increased mortality.[22]

Although such comparisons may be susceptible to confounding by failure to fully control for underlying severity of illness, the findings seem biologically plausible based on differences in therapy for MSSA and MRSA. Vancomycin, which has been the prevailing treatment option for serious MRSA infections, appears to be less bactericidal than beta-lactam agents against *S. aureus* and has been associated with higher treatment failure rates compared with antistaphylococcal beta-lactam antibiotics.[23] The suboptimal antistaphylococcal activity of vancomycin, which was likely the predominate treatment for most patients infected with MRSA in these studies, could explain why patients with MRSA infection seemed to have a worse outcome than patients infected with MSSA, who were more likely to have been treated with a beta-lactam antibiotic. If methicillin resistance is independently associated with a worse outcome among patients with SSI as these studies suggest, then a rising proportion of SSIs caused by MRSA could translate into worse overall clinical outcomes following *S. aureus* SSIs.

A significant proportional rise in MRSA infections among *S. aureus* SSIs carries with it important implications for prevention. If there is a growing population of surgical patients who have unrecognized MRSA colonization at the time of surgery, then there may be a growing population for whom standard surgical antimicrobial prophylaxis regimens consisting of beta-lactam agents may not be the appropriate choice. MRSA-colonized patients who receive a beta-lactam agent may be at increased risk of MRSA SSI. Identification of surgical patients who have MRSA colonization before surgery and use of vancomycin for prophylaxis in these cases might be an effective strategy for preventing MRSA SSI. However, more information is needed before changes in current surgical antimicrobial prophylaxis recommendations should be considered. As mentioned earlier, eradication of colonization may also be of benefit, but this approach requires further study.

The growth in the prevalence of MRSA among *S. aureus* SSIs is a reflection of the overall failure to control the spread of MRSA in many healthcare settings to date. Successful control of MRSA transmission could reduce the proportion of SSIs caused by this organism by two mechanisms. First, the number of surgical patients who are colonized before surgery would be reduced, decreasing the likelihood of an inadequate antimicrobial prophylaxis choice in those settings where preoperative screening for MRSA colonization is not done (eg, using a beta-lactam agent for a patient with unrecognized MRSA colonization). Second, for those patients who are not colonized with MRSA prior to surgery, successful control of transmission would reduce the risk of acquiring it from an external source during or after surgery. In the study by Perl et al., 60% of the *S. aureus* SSIs appeared not to have originated from nasal carriage of *S. aureus* by the patient,[15,17] suggesting an exogenous source. If a similar proportion of MRSA SSIs result from exogenous exposure, then controlling transmission is likely to have an important preventive impact. Although surgical patients can be exposed to MRSA while in the operating room, it seems likely that most exposures take place following surgery because the major reservoir for MRSA transmission in the healthcare setting is infected and colonized patients rather than healthcare workers.[24] Although the current understanding of the pathogenesis of SSIs would suggest that they usually occur as a result of intraoperative contamination of the surgical site, a recent study suggests that postoperative factors may play a role in the development of MRSA SSIs. Manian et al.[25] performed a retrospective cohort study of 270 patients who developed SSI to identify factors associated with MRSA SSI. Overall, 77 (28.5%) of the SSIs were caused by MRSA. On multivariate analyses, only discharge to a long-term–care facility and receiving an antibiotic for more than 1 day postoperatively were independently associated with MRSA SSI. Of interest, lack of surgical prophylaxis with vancomycin was not independently associated with an increased risk of MRSA infection. These results suggest that events occurring in the postoperative period can influence the development of MRSA SSI. Preventing exposure to MRSA in the postoperative period might therefore be an important aspect of controlling MRSA SSI. However, regardless of whether MRSA exposures leading to SSI occur prior to surgery, during surgery, or after surgery, the rise in MRSA prevalence among *S. aureus* SSIs sends the same clear message: more effective methods of preventing transmission of MRSA in the healthcare setting should be implemented.

The articles on SSI in this issue of *Infection Control and Hospital Epidemiology* suggest that the proportion of SSIs caused by *S. aureus* has grown, and that MRSA accounts for a large part of this increase. A preliminary analysis of data from the NNIS System corroborates these findings. These observations are of particular concern given the serious impact of *S. aureus* infection on clinical outcome, especially among the elderly, the most rapidly growing surgical population. These trends also have important implications for prevention. Strategies that successfully prevent *S. aureus* SSI may have a significant impact on the overall infection-related morbidity and mortality following surgical procedures. More work is needed to better

define the role of and strategies for identification of *S. aureus* carriers prior to surgery, eradication of carriage, and optimizing surgical antimicrobial prophylaxis for patients who may harbor MRSA. In addition, more effective methods of preventing MRSA transmission in the healthcare setting should be implemented.

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