



# REDUCTION OF SURGICAL SITE INFECTIONS BY PRE-OPERATIVE ERADICATION OF THE STAPHYLOCOCCUS AUREUS CARRIER STATE: *A Paradigm Whose Time has Come*

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*- Leap, and the net will appear  
- Zen saying*

## ABSTRACT

*Staphylococcus aureus (SA) is, and has always been, the most important pathogen in surgical site infections (SSI) around the world. Pre-operative colonization with SA is a well-established risk factor for post-operative SSI. The strain of SA that causes the post-operative SSI is identical to the pre-operative colonizing strain in the vast majority of cases. Several strategies have been shown to eradicate the SA carrier state, including the use of intranasal mupirocin ointment and chlorhexidine soap baths. Well-designed studies have now established that the pre-operative implementation of these strategies reduces the incidence of post-operative SSI due to SA by about 50%. These strategies greatly reduce the morbidity associated with SSI. Now that insurers no longer reimburse the costs of caring for SSI, strategies to reduce and control the incidence of post-operative infections will be crucial to the financial stability of hospitals, and perhaps even to their survival.*

## THE STAPH AUREUS CARRIER STATE

New genomic amplification techniques have demonstrated that healthy human skin is colonized with about 500 million bacteria per square inch, including over 180 different species. In fact, for humans bacterial cells outnumber our own cells by 10:1.<sup>1</sup> Colonization of the anterior nares and skin of humans with SA occurs frequently. About 20% of normal humans are persistently colonized with SA in the nares, while another 30-50% are intermittently colonized. Increased rates of carriage are seen in patients with underlying co-morbidities, such as diabetes, chronic kidney disease, HIV infection, and chronic dermatitis. Multiple studies indicate that among carriers of SA, colonization with methicillin-sensitive SA (MSSA) remains about 5x as common as colonization with methicillin-resistant SA (MRSA).

## SURGICAL SITE INFECTIONS DUE TO STAPH AUREUS

The Centers for Disease Control and Prevention (CDC) estimates that SSI account for 22% of all health-care associated infections. Over 290,000 SSI occur in the U.S. each year, resulting in an estimated 8000 deaths and in almost \$10 billion in direct and indirect medical costs. SA is the most frequent pathogenic isolate in SSI in the U.S. and around the world.<sup>3</sup>

The relative risk of SSI is 2-9 times greater in carriers of SA than in non-carriers.<sup>2</sup> Furthermore, molecular epidemiology has demonstrated that the strain of SA that causes a post-operative infection is identical to the strain isolated from the nasal cavity pre-operatively in 85% of patients.<sup>4</sup> Thus, SSI due to SA are due to endogenous microbes. Not surprisingly, nasal carriage of SA is an independent risk factor for SSI in cardiac,<sup>5</sup> vascular,<sup>6</sup> and orthopedic implant surgery.<sup>7</sup>

In a tertiary care orthopedic study, SSI due to MSSA resulted in 14 extra days of hospitalization, subjected patients to additional surgical procedures, increased the cost of care by over 300%, and significantly impacted health-related quality of life.<sup>8</sup> In a national survey of surgical patients, SSI due to SA increased the cost of care per patient (in 2004 dollars) approximately \$34,000 for orthopedics, \$84,000 for cardiac surgery, and \$119,000 for neurosurgery.<sup>9</sup>

## MEASURES TO ELIMINATE SA COLONIZATION

### UNIVERSAL SCREENING AND ISOLATION

Based on the knowledge of the risk of infection due to SA colonization, many experts and policy makers called for early universal screening of hospital admissions for MRSA carriage when rapid polymerase chain reaction (PCR) technology first became available. However, when rapid detection and prompt isolation of patients failed by itself to decrease the rate of MRSA nosocomial infection in surgical patients,<sup>10</sup> research turned to detection followed by attempts at chemical decolonization.

## MUPIROCIN

Intra-nasal instillation of mupirocin (MP) ointment twice daily for five consecutive days has been demonstrated to eradicate the SA carrier state.<sup>11</sup> But despite initial success in dialysis patients,<sup>12</sup> other early studies failed to show a decrease in invasive SA infections in non-surgical patients as a group.<sup>13</sup>

In an early study of cardiac surgical patients, which was somewhat limited by the use of historical controls, pre-operative eradication of SA resulted in a significant reduction in SSI.<sup>14</sup> Subsequently, preoperative treatment of nasal carriers of SA was studied across multiple surgical specialties at the University of Iowa in the MARS study.<sup>15</sup> Though the use of MP preoperatively did not reduce the overall rate of SSI due to SA, it was reduced in the subset of patients who were SA carriers from 7.7% to 4.0% (odds ratio 0.49,  $P=0.02$ ). That same year, a study in orthopedic patients who were treated with MP from admission to surgery also found no reduction in the overall rate of SSI due to SA, but again, in the subset of patients who were nasal carriers of SA, the rate of endogenous SA infection with MP was one-fifth the rate in the placebo group (0.3% vs. 1.7%, relative risk 0.19).<sup>16</sup> A meta-analysis of 4 other qualifying randomized controlled trials involving 686 patients colonized with SA who underwent pre-operative MP treatment demonstrated a 45% reduction in SSI due to SA.<sup>17</sup>

## CHLORHEXIDINE

Because intranasal MP may not affect SA colonization outside of the face and chest, additional topical decolonization with chlorhexidine gluconate (CHX) has been evaluated, with the finding that it is effective in eradication of SA from skin surfaces.<sup>18</sup> In fact, CHX-alcohol has now been shown to be superior to providone-iodine for preoperative skin cleansing, resulting in a reduction of the rate of SSI from 16% to 9.5% in one study.<sup>19</sup> This approach is now recommended as the standard of care for surgical antisepsis by the CDC.

## COMBINING MUPIROCIN AND CHLORHEXIDINE IN SA CARRIERS

The next wave of literature in this important topic evaluated the use of both MP and CHX specifically in patients colonized with SA. Completion of the eradication therapy prior to surgery is an additional important feature of these more contemporary studies.

In elective orthopedic implant surgery, Kim et al studied 7019 patients who were screened pre-operatively for both MSSA and MRSA colonization. All SA-positive patients were treated with both MP and CHX. Compared to historical controls, the screened and treated patients demonstrated an institutional infection rate of 0.19%, a reduction from the pre-study rate of 0.45% ( $P=0.009$ ).<sup>20</sup> Specifically, the SSI rate with MSSA was reduced from 0.26% to 0.13%, while the rate of SSI due to MRSA was reduced from 0.18% to 0.06%.

In a similar study, Rao et al compared 321 SA nasal carriers to 2284 concurrent and 741 pre-intervention controls. SA carriers were treated with both MP and CHX as outpatients prior to their elective orthopedic procedures. The overall SSI rate decreased from 2.7% to 1.2% ( $P=0.09$ ) and there were no SA infections in the eradication therapy group.<sup>21</sup> From a purely cost-effectiveness standpoint, the high cost of orthopedic implant infections makes both the screen-and-treat as well as the treat-everyone approach cost-effective, even though the latter approach is not necessary or efficient.<sup>22</sup>

In a study of a broader array of both surgical and medical patients, Bode et al. screened 6771 patients for SA colonization on admission and a total of 1251 were polymerase-chain-reaction positive. 917 patients were enrolled and treated with MP and CHX and 88% underwent a surgical procedure. The overall infection rate in the MP-CHX group was 3.4%, compared with 7.7% in the placebo group (relative risk of infection 0.42). However, the reduction in infection in the MP-CHX group was even more pronounced for deep SSI (relative risk 0.21).<sup>23</sup>

A literature review on the use of MP and CHX in studies published between 2006 and 2008 concluded that treatment of proven carriers of SA with MP is an effective and cost-effective method to prevent SSI with SA.<sup>24</sup> In addition, this paradigm for the use of MP and CHX in orthopedic patients has been sanctioned by the American Academy of Orthopaedic Surgeons Patient Safety Committee.<sup>25</sup> Finally, a Cochrane Database Systematic Review of 3396 participants in 9 randomized controlled trials concluded that in nasal carriers of SA, the use of MP results in a statistically significant reduction in SA infections.<sup>26</sup>

## NEW LAB METHODOLOGY FOR SA DETECTION

Success in the 'screen and eradicate' paradigm requires the ability to rapidly detect nasal

colonization with both MRSA and the more common MSSA. While MRSA PCR methodology has been used for many years, the recent development and availability of the dual-target PCR for both MSSA and MRSA (Cepheid SA Nasal) will allow deployment of methods for accurate and rapid detection of these important pathogens.

#### CONCLUSIONS

The association between SA nasal colonization and SSI has long been established, and the ability to decolonize patients with MP and CHX is also well documented. Early studies on eradication of the SA

carrier state suffered from methodological flaws in both design and execution, which slowed the evolution of research in the field. Now, however, with the availability of rapid PCR dual-target detection of both MSSA and MRSA, combined with the use of complete preoperative courses of both MP and CHX, physicians finally can see the light at the end of the tunnel toward reducing SSI due to SA. Achieving this attainable reduction in both morbidity and health care costs cannot come soon enough, and will require a concerted effort on the part of physicians, laboratory directors, and hospital administration. All we have to do is have the courage to leap.

#### EDITOR'S NOTE

*An abbreviated version of the intranasal instillation of antibiotic ointment described by Dr. Kontra has been used on the Cardiac Surgery service at LGH for many years. We did something similar during my training and subsequent faculty position from 1969-1975 with Dr. Albert Starr (co-inventor of the Starr-Edwards valve, the first successful prosthetic heart valve) at the University of Oregon Medical School. It was Dr. Starr's policy to insert antibiotic ointment into the nares of preoperative open heart surgery patients the day before surgery. Carrying out this order was one of the duties of the Cardiac Surgery resident, and I never forgot it.*

*I called Dr. Starr last month to ask why he had instituted this policy long before there were any studies in the*

*literature to document its benefits. He told me that early in his experience at Oregon, which began in the late 1950's he encountered a series of infections after valve replacement. He sought advice from an outside Infectious Disease specialist, who carried out multiple cultures of the operating room environment and the patients, and recommended a series of steps including the intranasal instillations of antibiotic ointment. This was an era when penicillinase-resistant antibiotics were still generally effective.*

*Obviously, that long-forgotten consultant had an unerring instinct for the practical application of common sense—a most uncommon commodity.*

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