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**Question**

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Intraoperative Vancomycin Use in Spinal Surgery: Single Institution Experience and Microbial Trends

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Key Words: vancomycin, spinal infection, surgical site infection, spondylosis, degenerative disease

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Study Design: Retrospective Case Series

Objective: To demonstrate the microbial trends of spinal surgical site infections (SSI) in patients who had previously received crystallized vancomycin in the operative bed.

Summary of Background Data: Prior large, case control series demonstrate the significant decrease in SSI with the administration of vancomycin in the wound bed.

Methods: A single institution, electronic database search was conducted for all spinal surgery patients who had received prophylactic crystalline vancomycin powder in the wound bed. Patients with a prior history of wound infection, intrathecal pumps, or spinal stimulators were excluded.

Results: 981 consecutive patients (494 male, 487 female, mean age 59.4 years, range 16-95 years) were identified from January 2011 to June 2013. The average dose of vancomycin powder was 1.13 grams (range: 1-6 grams). 66 patients (6.71%) were diagnosed with a SSI of which 51 patients had positive wound cultures (5.2%). Of the 51 positive cultures the most common organism was Staphylococcus aureus. The average dose of vancomycin was 1.3 grams in the 38 cases where a gram-positive organism was cultured. A number of gram-negative infections were encountered such as Serratia marcescens, Enterobacter aerogenes, Bacteroides fragilis, Enterobacter cloacae, Citrobacter koseri and Pseudomonas aeruginosa. The average dose of vancomycin was 1.2 grams in 23 cases where a gram negative infection was cultured. 15 of the 51 (29.4%) positive cultures were polymicrobial. 8 (53%) of these 15 polymicrobial cultures contained three or more distinct organisms.

Conclusions

Prophylactic intraoperative vancomycin use in the wound bed in spinal surgery may increase the incidence of gram-negative or polymicrobial spinal infections. The use of intraoperative vancomycin may correlate with postoperative seromas, due to the high incidence of non-positive cultures. Large, randomized, prospective trials are needed to demonstrate causation and dose-response relationship.
Key Points:

1. Prophylactic intraoperative vancomycin powder may correlate with an increased incidence of gram-negative or polymicrobial spine infections, as well as postoperative seromas.

2. This report is the first, large series study of spinal surgery patients that gives credence to a potential concern that intraoperative vancomycin powder could select for gram-negative organisms.

3. Large, randomized, prospective trials are needed to elucidate causation, dose-response relationship and cost implications.
Mini Abstract

981 patients receiving intraoperative vancomycin were retrospectively reviewed, with 51 patients being culture-positive (5.2%). Many of these were infections were gram-negative and polymicrobial infections, giving credence to the concern that intraoperative vancomycin powder has a significant impact on microbial trends.
Introduction

Interest in quality improvement and cost-containment measures in spinal surgery is an ongoing driving force in evidence-based medicine. One obstacle to lowering healthcare cost in spine surgery is the not infrequent incidence of surgical site infection (SSI), with reports ranging from 0.7 to 11.9%. This poses a significant challenge for cost reduction in spinal surgery, as it is estimated that the escalated cost of care for an infected patient is up to four-times. This is especially significant since reimbursements are being phased out for postoperative SSI.

Retrospective evidence has demonstrated the decrease in incidence of SSI with the use of vancomycin in the wound bed. Because prior estimates place the additional costs of a SSI at 33,705 USD per infection, the use of vancomycin prophylaxis in the wound may save up to 438,165 US Dollars per 100 patients.

The present retrospective case series serves to highlight the characteristics of vancomycin powder use intraoperatively in a large series, with a comprehensive characterization of postoperative infections in patients who have been treated with vancomycin to their spinal wound. Because of a theoretical concern for growing organism resistance with the aggressive use of broad-spectrum antibiotics, the authors hypothesize that a similar phenomenon could occur with the use of wound vancomycin. With the widespread use of vancomycin intraoperatively, a survey of the postoperative infections in patients treated with vancomycin may reveal superinfections with uncommon organisms, a result of selective pressures exerted by vancomycin on ambient flora.

Methods

**Electronic Search**

Institutional review board approval was obtained for this study. A retrospective electronic chart review was conducted from January 2011 to June 2013 for all spinal surgery patients receiving intraoperative vancomycin at a single institution. Patients who underwent spinal procedures for degenerative disease, trauma, pain, and scoliosis were included. Mean age, gender, BMI, and surgical procedure were recorded.
A query was performed for all patients who underwent spinal surgery and had also received dry, crystallized vancomycin in the wound bed. Per attending preference, either 1 or 2 grams of crystallized vancomycin was evenly distributed through the subfascial and epifascial layers; this was often a determination based on the size of the wound bed. In rare cases, up to 6 grams were reportedly used. Preoperative antibiotics were administered one hour prior to skin incision with 1000 mg of intravenous cefazolin. Patients who had a cephalosporin allergy underwent intravenous infusion with 1000 mg vancomycin (2000 if over 70kg).

Postoperative subfascial and epifascial drainage catheters were removed at the discretion of the spinal surgeon which varied typically from 3-5 days postoperatively or when drainage output decreased below 30cc in an 8 hour period. Postoperative antibiotics are standardized for all surgical patients with cephalosporin given two more doses every 8 hours and in the case of vancomycin, one more dose was given twelve hours after the first dose.

The incidence and characteristics of patients with surgical site infections were evaluated. In all cases, surgical site infections underwent antibiotic irrigation and debridement of devitalized tissue. Risk factors in those treated with vancomycin who developed a postoperative surgical site infection (SSI) were evaluated. For patients who had a postoperative infection, organisms cultured and their frequency were characterized. All patients who went to the operating room and had a surgical debridement were considered a SSI. Postoperative cultures that were negative were still considered as a wound infection, despite the results, given the possibility that postoperative vancomycin could contaminate the culture.

Exclusion criteria included any patient with a history of a prior spinal infection as well as those whose primary indication was chronic pain management, including intrathecal pumps and spinal cord stimulators. Comparison was made to recent historical data on overall spine infections from previously published literature about overall spine infections.

SSI Criteria and Decision-making Algorithm
The decision to undergo a wound washout, and thus the criteria for diagnosis of a SSI was ultimately at the discretion of the attending surgeon. For all patients with wound drainage or minimal breakdown with drainage, irrigation with debridement and definitive closure in the operating room was performed. In the absence of wound drainage, the clinical decision to proceed with a washout was performed on a case-by-case basis from a combination of the following signs, symptoms, and objective evidence: fevers, persistent pain, erythema, MRI evidence of infection, or elevated laboratory markers such as erythrocyte sedimentation rate, c-reactive protein, and white cell count.

Statistical Analysis

Organism distribution was evaluated from both vancomycin cohort and historic control data with a two-tailed t-test. P-values of ≤ 0.05 were considered statistically significant. Statistical analysis was carried out with a statistical software package (JMP v 8.0.1, SAS institute 2012).

Results

In an electronic search of the hospital medical record system, 981 consecutive patients from Jan 2011 until June 2013 underwent spinal surgery and had received intraoperative vancomycin in the skin edges, muscle, fascia, and wound bed, without intentional mixing into the bone graft (494 male, 487 female, mean age 59.4 years, range 16-95 years). The average dose of vancomycin powder was 1.13 grams (Range: 0.5-6 gm). The most common doses for the patients was 1 gram (849 patients) and 2 grams (123 patients). The mean BMI of the patient population was 30.27. Table 1 lists the indications for the surgical procedures, although there was an overlap of degenerative diseases as well as other indications. Overall in this series, 66 patients (6.71%) were diagnosed with a surgical site infection (SSI). All of these 66 patients received a wound irrigation, debridement, and drain placement per the aforementioned protocol.
All patients who returned to the operating room for postoperative infection were cultured intraoperatively. Fifty-one patients had positive wound cultures (5.2%). In 15 patients, no organism growth was noted over 72 hours of culturing. The most common organism cultured intraoperatively was *Staphylococcus aureus* (table 2). A number of gram-negative infections were encountered such as *Serratia marcescens, Enterobacter aerogenes, Bacteroides fragilis, Enterobacter cloacae, Citrobacter koseri, Pseudomonas aeruginosa*.

15 of the 51 (29.4%) positive-cultures were polymicrobial. 8 (53%) of these 15 polymicrobial cultures contained three or more distinct organisms. Of the positive wound cultures, the majority were cultured from the lumbar spine (n=35, 67%), followed by the thoracic (10, 20%) and cervical spine (6, 13%) (table 3). In the patients who were cultured for wound infection, the most common preoperative indication for the index surgery was degenerative disease: spinal stenosis, degenerative disk disease, spondylolisthesis, and cervical spondylotic myelopathy. Trauma was an indication in nine of the positively cultured patients.

**Arthrodesis**

Out of 981 total patients, 865 patients had an instrumented fusion, and 187 underwent only a decompression most often for a lumbar disc herniation. The mean number of levels fused was 2.4 (Range: 1-16).

All 981 patients underwent a decompressive surgery. There was no significant association between the number of fusion levels and incidence of SSI (table 5).

Discussion

Evidence from previously reported case series clearly demonstrates the utility of surgical site vancomycin for lowering spinal wound infection rates (table 5). Vancomycin powder appears to be effective for instrumented and non-instrumented fusions equally, as well as for decompressions. Prior case series demonstrated efficacy regardless of the mixture of vancomycin in the bone graft or not.  

**Prior Studies on Intraoperative Vancomycin Use**

Strom et al. evaluated 253 patients who underwent a lumbar decompression and fusion and had received 1 gram of intraoperative vancomycin. Compared to well-matched controls at the same institution, a
dramatic reduction in the infection rate was noted (11% to 0%, P<0.0001). This study excluded superficial wound infections due to the variability in the presentation. Vancomycin powder was applied to the muscle, fascia, and deep tissue, but not intermingled with the bone graft. This study had a well-matched control group. The authors also examined the vancomycin levels in blood, finding a low level, suggestive of minimal systemic absorption, and a high-level in the postoperative drains to day 3, evidence of a lasting antimicrobial effect. There were no adverse effects related to vancomycin use.

Sweet et al. evaluated the use of intraoperative vancomycin in the thoracolumbar patient population, expanding the cohort size to 911, with a significantly larger 2 gram vancomycin dose. One gram of vancomycin was mixed with the bone graft at least 15 minutes prior to placement, with the remaining vancomycin spread evenly in the wound. Similar results were obtained, with dramatic reduction in deep wound infection (2.6 to 0.2%). Like previous studies, the superficial wound infections were excluded.

O’Neill and colleagues reported their experience in a retrospective review of 216 patients who underwent posterior instrumented fusion for traumatic spine fractures, finding a decrease in infection from 13% in controls to 0% in the treatment group which had received 1 gram of intraoperative vancomycin to the wound bed, without mixing the vancomycin in the bone graft. In this study, superficial infections were not excluded, where in the control group, there were 2 superficial, and 5 deep wound infections that required operative irrigation and debridement.

Molinari and colleagues evaluated their experience with 1512 patients who underwent prophylactic vancomycin application to spinal wounds, resulting in only 15 infections (0.99%). This number is influenced by the fact that only deep infections were reported, as they report that 1 gram of vancomycin was only placed beneath the fascia, and like most other studies was not mixed in with the bone graft. There was no control group for comparison.
Our reported infection rate of 6.4% was of those patients who went to the operating room with an infection. Those patients who were cultured and had an identified organism totaled 5.2% (where seronegative collections were excluded). With comparison to one historic control cohort study from 2005 to 2009, a mean incidence of spine infection of 3.4% was reported, with a range as high as 4%. The lower rate of spine infection mentioned in the previously reported series as well as from other previous series (table 4) was most likely accounted for by the less stringent selection criteria in this present study. Additionally, in our present study, the administration of vancomycin was at the discretion of the surgery which undoubtedly was biased towards higher risk patients. The purpose of this manuscript was to capture potential infections after use of intraoperative vancomycin with a hypothesis that the selective pressures of vancomycin could lead to the emergence of gram-negative and atypical gram-positive organisms (table 2).

Comparison to a previous report by Rao et al in 2008, evaluated the outcomes of 1587 patients who underwent spinal surgery that year, finding 57 deep SSI (3.7%, P=0.049). Interestingly, in this series of patients who did not have vancomycin powder, 67% of the infections contained Staphylococcus aureus, while in our present series, S. Aureus was cultured 57% of the time. Gram-negative organisms occurred with a greater frequency in the vancomycin treatment group (60% vs. 21%, P =0.0001). Polymicrobial infections were encountered 15% of the time in prior historical controls and 19% in our present series (P=0.9638) (table 2). Prior publications exclude superficial infections for the reason of clinical ambiguity and the difficulty in culturing the wound without contamination with the skin flora. Since cultures were taken in the intraoperative setting, where the skin has been sterilized and the culture taken from the fascia directly, as well as subfascial soft tissues, it is unlikely that normal skin flora contaminated our cultures. In all, as concluded in systematic reviews of SSI in spinal surgery, lack of standardized definitions of SSI and inconsistencies with methodology and error reporting introduce significant bias and may serve as the source of variation in these SSI rates.

In our series, we find an overabundance of gram-negative organisms (Table 2), lending support to our hypothesis that intraoperative vancomycin provides a selective pressure resulting in increased prevalence of gram-negative and polymicrobial wound infections. In our two cases of fungal infection, the patients were not diabetic, nor did they have prior radiation, or an immunocompromised status. One future consideration would be to
broaden the antibiotic coverage, adding another antibiotic to vancomycin in the wound to cover these gram negative organisms. This is likely a safe measure as prior studies have shown the minimal systemic absorption and high concentration locally by measurement in the drain output.

Study Limitations

Our study is limited by the lack of a control cohort. However, the purpose was not to repeat a prior vancomycin control cohort study as was previously performed. Given that a recently published series on the rate of spine infection existed, this was felt adequate for a historical figure of comparison. The present study, however, differs from this previously published data in our selection criteria. This study includes different spinal surgeons as well as a more diverse sample of patients who underwent intraoperative administration of vancomycin. Also, selection bias from the annual fluctuations in infection rates that occur is relevant in this comparison. Here, we compare a prior 12 month historic control cohort to an 18 month, nonconsecutive cohort.

In addition to the significant increase in gram-negative organism on historic controls, a preponderance of the literature reports little if any gram-negative or polymicrobial infections once vancomycin powder is introduced. This discordance is important since it could also demonstrate the emergence of drug-resistant organisms. More prospective studies need to be done to demonstrate this cause-effect relationship.

Conclusion

Prophylactic Intraoperative vancomycin use in the wound bed in spinal surgery may increase the incidence of gram-negative or polymicrobial spinal infections. The use of intraoperative vancomycin may correlate with postoperative seromas. Large, randomized, prospective trials are needed to elucidate causation, dose-response relationship and cost implications.
References

### Table 1. Surgical Indications by Diagnosis

<table>
<thead>
<tr>
<th>Indication</th>
<th>N, uninfected</th>
<th>%</th>
<th>N, Diagnosis of SSI</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degenerative disk disease</td>
<td>143</td>
<td>10.27</td>
<td>2</td>
<td>1.82</td>
</tr>
<tr>
<td>Stenosis</td>
<td>478</td>
<td>34.34</td>
<td>51</td>
<td>46.36</td>
</tr>
<tr>
<td>Spondylolisthesis</td>
<td>322</td>
<td>23.13</td>
<td>28</td>
<td>25.45</td>
</tr>
<tr>
<td>Deformity Correction</td>
<td>209</td>
<td>15.01</td>
<td>14</td>
<td>12.73</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>36</td>
<td>2.59</td>
<td>2</td>
<td>1.82</td>
</tr>
<tr>
<td>Trauma</td>
<td>90</td>
<td>6.47</td>
<td>9</td>
<td>8.18</td>
</tr>
<tr>
<td>Adjacent level disease/pseudoarthrosis</td>
<td>62</td>
<td>4.45</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Others*</td>
<td>52</td>
<td>3.74</td>
<td>4</td>
<td>3.64</td>
</tr>
</tbody>
</table>

*Other secondary or multifactorial pathologies include: spondylosis (34), myelopathy (31), arachnoid cyst/pseudomeningocele (9), OPLL (3), ankylosing spondylitis (5), central cord syndrome (6), cauda equina syndrome (9), spondyloptosis (1), charcot spine (1).

### Table 2. Cultured Organisms from Culture positive Surgical Site Infections*

<table>
<thead>
<tr>
<th>Organism</th>
<th>N, Cultured (n=51)</th>
<th>Historic Control (n=57)</th>
<th>P = 0.0490</th>
</tr>
</thead>
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<tr>
<td><strong>Gram Positive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus (MSSA)</em></td>
<td>15</td>
<td>25</td>
<td>0.1199</td>
</tr>
<tr>
<td><em>Streptococcus mutans</em></td>
<td>1</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td><em>Coagulase negative staphylococcus</em></td>
<td>17</td>
<td>16</td>
<td>0.5516</td>
</tr>
<tr>
<td><em>Enterococcus faecalis (Group D streptococci) (VRE)</em></td>
<td>1</td>
<td>5</td>
<td>0.1206</td>
</tr>
<tr>
<td>MRSA</td>
<td>11</td>
<td>11</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Gram Negative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corynebacteria sp.</td>
<td>1</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>9</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>7</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Proteus mirabilis/other proteus species</td>
<td>7</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>2</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td><em>Enterobacter aerogenes</em></td>
<td>1</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td><em>Serratia marcescens</em></td>
<td>1</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td><em>Bacteroides fragilis</em></td>
<td>1</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td><em>Enterobacter cloacae</em></td>
<td>1</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td><em>Citrobacter koseri</em></td>
<td>1</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Culture negative</strong></td>
<td>15</td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Fungal</strong></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Polymicrobial</strong></td>
<td>15</td>
<td>17</td>
<td>0.9638</td>
</tr>
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</table>

### Table 3: Positive Wound Culture by Region
<table>
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<tr>
<th>Surgical Treatment</th>
<th>N</th>
<th>Incidence of SSI</th>
</tr>
</thead>
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<tr>
<td>Arthrodesis</td>
<td>865</td>
<td>45 (88%)</td>
</tr>
<tr>
<td>Decompression</td>
<td>925</td>
<td>6 (12%)</td>
</tr>
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</table>

### Table 4: SSI and Arthrodesis

<table>
<thead>
<tr>
<th>Manuscript Description</th>
<th>Author(s)</th>
<th>Journal</th>
<th>Year</th>
<th>N</th>
<th>Design</th>
<th>Spine</th>
<th>Method</th>
<th>Infection Rate Control</th>
<th>Infection Rate SSV</th>
<th>P Value</th>
<th>Add'l Outcome</th>
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</thead>
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<tr>
<td>Comparative effectiveness of vanco in spinal wounds</td>
<td>Godil et al</td>
<td>JNS Spine</td>
<td>2013</td>
<td>110</td>
<td>Retrospective</td>
<td>C</td>
<td>SSV vs. control</td>
<td>13% control</td>
<td>O%</td>
<td>0.02</td>
<td>33,705 USD per infection, 438,165 USD saved per 100 patients with SSV</td>
</tr>
<tr>
<td>Intrawound Vanco for TL Fusion prophylaxis</td>
<td>Sweet</td>
<td>Spine</td>
<td>2011</td>
<td>173</td>
<td>Retrospective</td>
<td>TL</td>
<td>SSV vs. control</td>
<td>2.6</td>
<td>0.2</td>
<td>&lt;0.0001</td>
<td>Control group org- s. aureus/SSV infections - no organism</td>
</tr>
<tr>
<td>Lumbar laminectomy and fusion with routine application of vancomycin</td>
<td>Strom et al</td>
<td>Clin Neurol and Neurosurg</td>
<td>2013</td>
<td>253</td>
<td>Retrospective</td>
<td>Lumbar</td>
<td>SSV vs. control</td>
<td>11</td>
<td>0</td>
<td>0.0008</td>
<td>Significant reduction in infection with routine vancomycin in use</td>
</tr>
<tr>
<td>Reduced SSI in instr. Fusions for trauma in posterior</td>
<td>O’Neill et al</td>
<td>Spine J</td>
<td>2011</td>
<td>110</td>
<td>Retrospective</td>
<td>CTL sp</td>
<td>SSV vs. control</td>
<td>13</td>
<td>0</td>
<td>0.02</td>
<td>Significant reduction in infection</td>
</tr>
<tr>
<td>spinal surgery</td>
<td>Molinari</td>
<td>Eur Sp J</td>
<td>2012</td>
<td>1512</td>
<td>Retrospective</td>
<td>A or P, CTL sp</td>
<td>All w/ SSV</td>
<td>N/A</td>
<td>0.99%</td>
<td>N/A</td>
<td>Infection rate for instrumented vs. uninstrumented 1.20 vs. 0.82%, respectively. S. aureus was most isolated 6/15 infections</td>
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