Does Empiric Antibiotic Therapy Change Hand Infection Outcomes? Cost Analysis of a Randomized Prospective Trial in a County Hospital

Jeffrey E. Janis, M.D.
Daniel A. Hatef, M.D.
Edward M. Reece, M.D.
Corrine Wong, M.D.

Columbus, Ohio; Houston and Dallas, Texas; and Phoenix, Ariz.

Background: The incidence of community-acquired methicillin-resistant *Staphylococcus aureus* infections is rising at an alarming pace. Effective treatment has historically involved early débridement and antibiotic administration. This study was designed to prospectively determine the effectiveness of empiric therapy in treating hand infections.
Methods: A prospective randomized trial was conducted at a level I county hospital. Patients with a hand infection received either empiric intravenous vancomycin at admission or intravenous cefazolin. Outcomes were tracked using severity of infection, appropriate clinical response, and length of stay. Cost-effectiveness was calculated using total cost for each patient in both groups. Statistical analyses were performed.
Results: Forty-six patients were enrolled in the study. Twenty-four were randomized to cefazolin (52.2 percent) and 22 (47.8 percent) to vancomycin. There was no statistical difference between cost of treatment ($p < 0.20$) or mean length of stay ($p < 0.18$) between the groups. Patients randomized to cefazolin had higher mean costs of treatment compared with patients who were randomized to vancomycin ($p < 0.05$). Patients with more severe infections had more expensive mean costs of treatment ($p < 0.0001$) and longer mean length of stay ($p = 0.0002$). Near the end of the study, the incidence of community-acquired methicillin-resistant *S. aureus* at the authors' county hospital was discovered to be 72 percent, which caused the study to be terminated prematurely by the institutional review board because of the high incidence precluding further randomization.
Conclusions: Appropriate early treatment for methicillin-resistant *S. aureus* has not been definitively established. No difference in outcome using cefazolin versus vancomycin as a first-line agent was identified. (*Plast. Reconstr. Surg.* 133: 511e, 2014.)

Physicians and patients have engaged in a dangerous game of brinkmanship with microorganisms since the advent of penicillin in 1929.[1] Widespread use of antibiotics leads to resistant patterns in bacteria, as was first noted by the late 1940s.[2–4] There is no way that Fleming could have foreseen the storm that lay ahead of him after his landmark discovery, yet resistance constantly engages therapy in this molecular arms race. One front of this battle revolves around methicillin resistance in *Staphylococcus aureus* species. There has been a recent explosion in the incidence of both hospital- and community-acquired methicillin-resistant *S. aureus*.[5–7] This has begun to reach alarming proportions, with some investigators reporting over 50 percent of studied inpatients colonized with the resistant organism.[8]

From the Department of Plastic Surgery, The Ohio State University Medical Center; the Michael E. DeBakey Department of Surgery, Division of Plastic Surgery, Baylor College of Medicine; the Arizona Center for Hand Surgery; and the Department of Plastic Surgery, University of Texas Southwestern Medical Center.
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Increasing prevalence of community-acquired methicillin-resistant *S. aureus*[9] has been accompanied by an increase in bacterial soft-tissue infections.[10] Among these, hand infections have been reported as among the highest of involved anatomical regions, with incidences ranging from 73 to 78 percent.[11,12]

Staphylococcal species are most commonly associated with hand infections,[13] and treatment algorithms involving hand infections have been proposed.[12] The mainstay of treatment has classically involved early, thorough operative débridement and broad-spectrum antibiotic administration.[14,15] Since the start of what can only be described as a "methicillin-resistant *S. aureus* epidemic," what has not been looked at is the role of early empiric antibiotic activity. When considering the lessons learned with penicillin resistance,[2,3,16] the practitioner must select appropriate antibiotics without contributing to developing resistance. Caution must be used before administering penultimate and ultimate antibiotic therapy that may very well become obsolete if practice patterns continue without careful thought and evidence-based therapy.

Hand infections present an ideal front for investigation of the battle over infected wounds balanced by antibiotic overuse. The effectiveness of broad-spectrum antibiotic administration in acute hand infections is unknown and may be unnecessary when thorough débridement is used. To clarify the optimal approach to empiric antibiotics in hand infections, a prospective randomized trial was designed to examine efficacy and cost of two different antibiotic regimens in acute hand infections at a busy county hospital. It was the authors' null hypothesis that there would be no difference between cefazolin and vancomycin in the treatment of hand infections, emphasizing the primary importance of surgical drainage in the management of these patients.

PATIENTS AND METHODS

A randomized prospective trial was designed and submitted to the Institutional Review Board of the University of Texas Southwestern Medical Center and Parkland Memorial Hospital. Forty-two consecutive patients presenting to the Plastic Surgery Service with acute hand infection were evaluated for potential entry into the study. Population characteristics are listed in Table 1. Patients eligible for the study included acute hand infection necessitating admission, age at least 18 years, plan for operative débridement, and ability to provide consent. Exclusion criteria involved patients receiving more than one dose of antibiotics before consultation, known causative organism, medical contraindication to therapy, allergy to study medications, systemic infection, immunodeficiency, pregnancy, breastfeeding, and county prisoners (Table 2). Patients were examined in the emergency department and the encounter characteristics were documented. Recorded data included type of infection, anatomical location, temperature, white blood cell count, presence of cellulitis, purulence, and necrotic tissue. These different factors were used to calculate a hand infection severity score, with points assigned for different signs and symptoms (Table 3). Nonoperative cellulitis alone was an exclusion criterion for the study, and these patients were admitted to medicine service and co-managed with rest, immobilization, elevation, and intravenous antibiotics.

Table 1. Population Characteristics

	Cefazolin	Vancomycin
No.	24	22
Mean age, yr	43.7	35.0
Sex		
Male	22	16
Female	2	6
Severity score	2.08	1.82
MRSA-positive cultures	14	19

MRSA, methicillin-resistant *Staphylococcus aureus*.

A goal of 100 enrolled patients was set before the study. The desired sample size was calculated using an online statistical calculator (https://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/samplesizecalculators.aspx). Patients were randomized by blinded sealed envelope into one of two arms. In the first, patients were given 1 g of intravenous vancomycin every 12 hours. In the second, patients were given 2 g of intravenous cefazolin every 8 hours. Each therapeutic arm was

Table 2. Inclusion and Exclusion Criteria

Criteria
Inclusion
Admitted hand infection
Age ≥18 yr
Operative débridement
Ability to provide consent
Exclusion
More than one preconsultation antibiotic dose
Known causative organism
Medical contraindication to therapy
Allergy to study medications
Systemic infection
Immunodeficiency
Pregnancy
Breastfeeding
County hold prisoners

Table 3. Severity Score Tabulation

	No. of Points
Cellulitis, edema, rubor, local infective signs	1
Temperature >101.5°F	1
Purulent drainage	1
Necrotic tissue	1

initiated in the emergency department. Antibiotic choice did not influence the decision for operative drainage with concurrent wound cultures. Empiric antibiotic regimens continued until culture and sensitivity results were returned. At this point, antibiotics were altered to administer culture-directed antimicrobial therapy.

Patients were followed as inpatients, and outcomes were recorded. Clinical efficacy was measured by number of days to a successful response to treatment (i.e., decreased swelling and tenderness, increased range of motion, resolution of leukocytosis, resolution of tachycardia, fever, or other clinical signs of infection), length of hospital stay, and number of operations. Cost-effectiveness of each empiric arm was also measured as determined by the total cost of in hospital treatment. This was calculated by the central billing office at Parkland Hospital, and included floor bed stay charges, nursing time, operating room time and supplies, and pharmacy and floor supplies. Statistical analysis was performed using GraphPad software (GraphPad Software, Inc., La Jolla, Calif.).

RESULTS

Forty-six patients were admitted to the study. The mean age of the patients was 39.5 years; 38 of the enrollees were male (82.6 percent). All were right handed. Thirty-one of the infections (67.4 percent) involved the patient's right hand. Twenty-four of the patients (52.2 percent) were unemployed at the time of enrollment. Thirty-eight of the patients had no form of insurance at the time of enrollment (82.6 percent); four had commercial insurance and/or worker's compensation (8.7 percent); and four had Medicaid or Medicare (8.7 percent). Twenty-two of the patients were randomized to vancomycin (52.2 percent), and the other 24 were administered cefazolin (47.8 percent). All patients underwent immediate débridement either in the emergency room ($n = 42$) or, in the case of flexor tenosynovitis, in the operating room ($n = 4$). There were no second operations for further débridement and drainage. The project was terminated prematurely by the institutional review board because of concern that empiric therapy consisting of cefazolin would be inadequate and inappropriate in treating the developing high incidence of methicillin-resistant *S. aureus* hand infection in this county hospital setting.

Infection Characteristics and Culture Results

Twenty-eight of the hand infections presented as abscesses (60.9 percent) (Fig. 1). Flexor tenosynovitis was the second most commonly treated hand infection, seen in four of the patients. The most common location was the digits, in 54.3 percent of enrolled patients (25 patients) (Fig. 2). Eighteen infections (39.1 percent) were assigned a severity score of 1 (with 1 being lowest and 4 being highest) (Table 3); 16 (34.8 percent) were assigned a severity score of 2; eight (17.4 percent) were assigned a severity score of 3; and four were assigned a severity score of 4 (8.7 percent) (Fig. 3). The majority of wound cultures were positive for methicillin-resistant *S. aureus* [$n = 33$ (71.7 percent)] (Fig. 4). Identification/speciation of the cultures typically was reported 48 hours after culture specimens were sent.

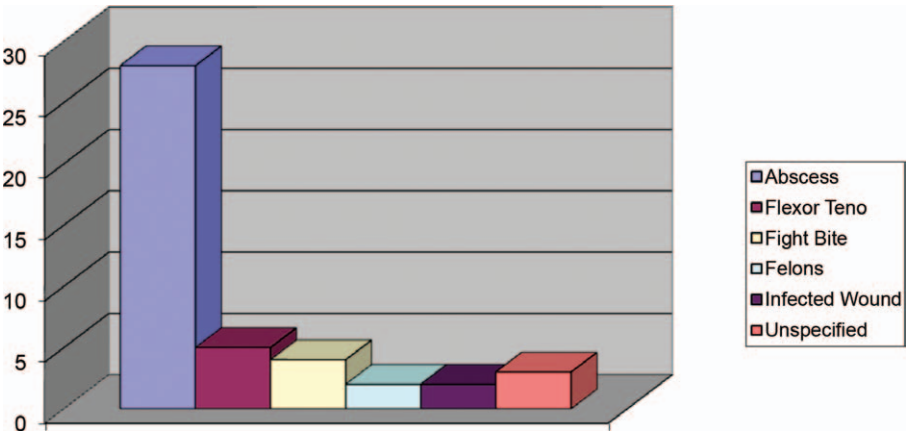

Fig. 1. Infection types.

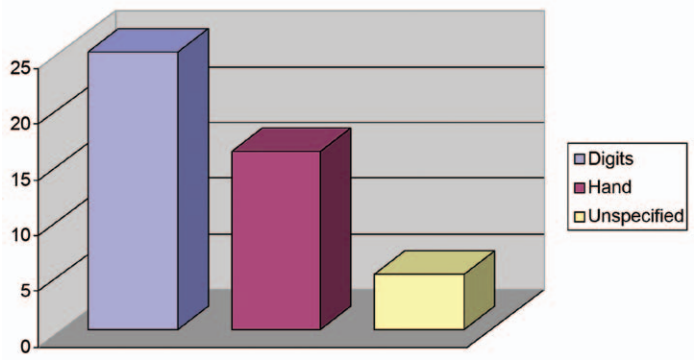

Fig. 2. Infection location.

Length of Stay and Cost of Treatment

The group of patients randomized to cefazolin ($n = 22$) had a mean length of stay of 5.75 days (SEM, 1.00 day) (Fig. 5). Patients randomized to vancomycin ($n = 24$) had a mean length of stay of 4.23 days (SEM, 0.52 day). The *t*-test comparison between groups revealed no difference ($p < 0.20$). Controlling for the severity score with a two-way analysis of variance, there was no statistical difference with choice of antibiotics concerning length of stay ($p < 0.17$).

There was no statistical difference in cost of treatment between the two antibiotic groups. Patients randomized to cefazolin had a mean cost of treatment of $6693.23 (SEM, $1370.90) (Fig. 6). Patients randomized to vancomycin had a mean cost of treatment of $4589.41 (SEM, $589.26). The *t*-test comparison of means revealed no difference between these two groups ($p < 0.18$). A two-way analysis of variance was performed controlling for severity of infection and did not reveal statistical significance ($p < 0.12$).

When the group of patients assigned to cefazolin was further analyzed, with all patients in this group who did not have methicillin-resistant *S. aureus*–positive cultures excluded, the mean cost of treatment was $7519.92 (SEM, $5843.12), and the mean length of stay was 6.36 days (SEM, 5.65 days). The mean cost of treatment for this group was significantly higher compared with the group of patients receiving vancomycin ($p < 0.05$). Comparison to the vancomycin patients regarding the mean length of stay did not reach statistical significance ($p < 0.13$).

There was no difference in outcomes between the two groups of assigned antibiotics with respect to infection severity. Patients with a lower severity score (i.e., 1 or 2) in the cefazolin group ($n = 16$) had a mean length of stay of 3.90 days (SEM, 0.40 day). The patients in the lower severity group receiving vancomycin ($n = 18$) had a mean length of stay of 3.80 days (SEM, 0.40 day) ($p = 1.00$). Cost analysis of hospital stay for low-severity-score treatment groups showed no difference. The low-severity cefazolin group had a mean treatment cost of $3921.00 (SEM, $626.50), whereas the low-severity patients on vancomycin had a mean treatment cost of $3988.50 (SEM, $497.90) ($p = 1.00$).

Patients assigned higher severity scores (3 or 4) demonstrated no differences in outcome between the two antibiotic groups. Patients with a higher severity score randomized to cefazolin

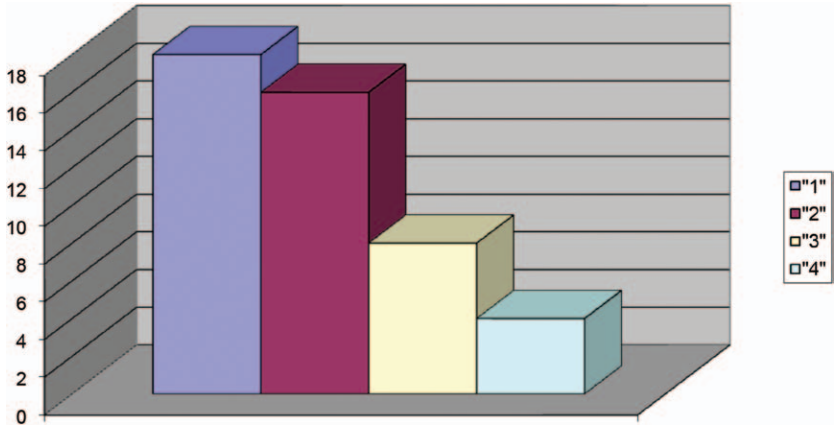

Fig. 3. Severity score.

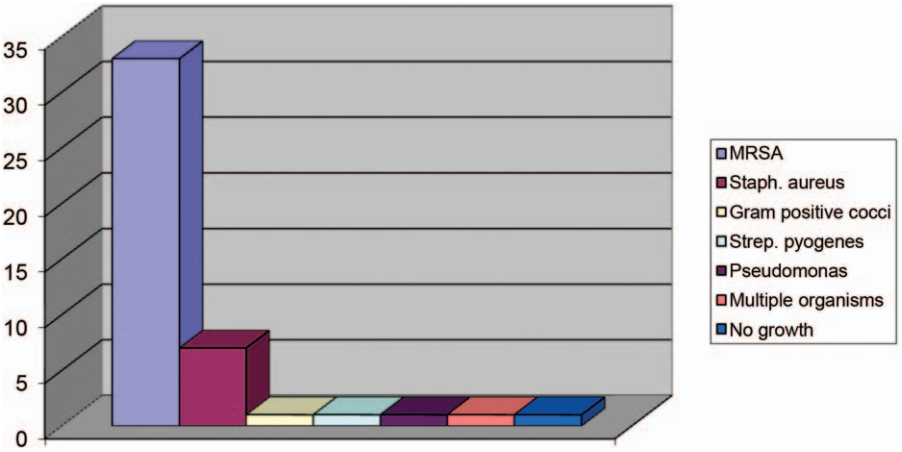

Fig. 4. Culture results. *MRSA*, methicillin-resistant *Staphylococcus aureus.*

(n = 8) had a mean length of stay of 9.50 days (SEM, 2.50 days), whereas the patients on vancomycin (n = 4) had a mean length of stay of 6.30 days (SEM, 2.10 days) (p = 0.508). The mean cost of treatment for the higher severity score patients on cefazolin (n = 8) was $12,237.70 (SEM, $3202.50); the mean cost of treatment of the higher severity score patients on vancomycin (n = 4) was $7293.30 (SEM, $2017.00) ($p$ < 0.57).

Infection severity was demonstrated to be a statistically significant indicator of both length of stay and cost of treatment regardless of antibiotic therapy. Patients who were assigned a severity score of 1 or 2 (n = 34) had a mean length of stay of 3.82 days (SEM, 0.28 day); patients with severity scores of 3 or 4 (n = 12) had a mean length of stay of 8.42 days (SEM, 1.79 days) (Fig. 7). The t test for means revealed a statistically significant difference (p = 0.0002).

Cost of treatment was also significantly different as a result of infection severity. Patients with infections of severity score 1 or 2 (n = 34) had a mean cost of treatment of $3956.77 (SEM, $389.34), whereas severity scores 3 or 4 (n = 12) had a mean cost of treatment of $10,589.54 (SEM, $2283.59) (Fig. 8). This proved to be statistically significant (p < 0.0001).

DISCUSSION

Since the advent of penicillin, the physician and patient have struggled with treatment of infection in the face of increasing bacterial resistance. Hand infections have been no exception. Nowhere is this more poignant than in the case of methicillin-resistant *S. aureus* infection. Community-acquired methicillin-resistant *S. aureus* is usually differentiated from hospital-acquired methicillin-resistant *S. aureus* by having the staphylococcal cassette chromosome (SCC) *mec* IV gene (hospital-acquired methicillin-resistant *S. aureus* have SCC*mec* I, II, II, and V genes).[17] The smaller size of the SCC-*mec* IV gene allows wider susceptibility of the community-acquired methicillin-resistant *S. aureus* to antimicrobials compared with hospital-acquired methicillin-resistant *S. aureus.* Furthermore, community-acquired methicillin-resistant *S. aureus* frequently contains the Panton-Valentine leukocidin

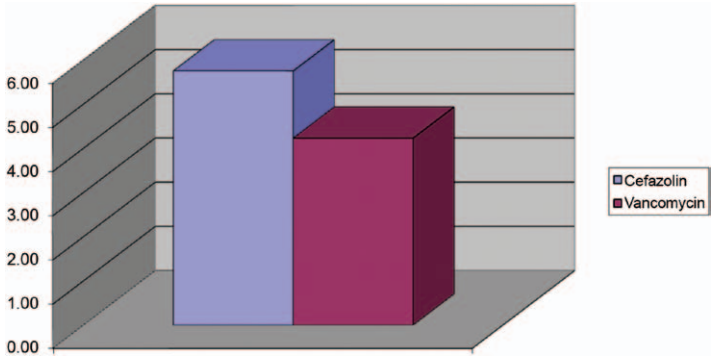

Fig. 5. Mean length of stay per antibiotic randomized to cefazolin or vancomycin.

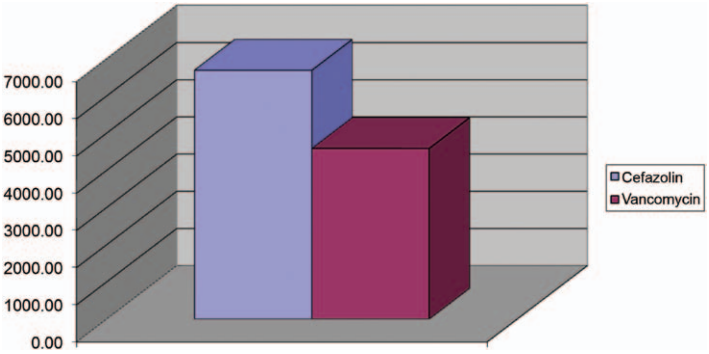

Fig. 6. Mean cost per antibiotic randomized to cefazolin or vancomycin.

gene, which gives the *S. aureus* a necrotizing, membrane-destructive cytotoxin that targets leukocytes and erythrocytes, thus allowing local invasiveness in soft-tissue infections.[7,17–19]

The incidence of community-acquired methicillin-resistant *S. aureus* hand infection is known to be rising.[20] Imahara and Friedrich have reported in their study that the risk of having a methicillin-resistant *S. aureus* hand infection was found to be 41 percent higher each progressive calendar year relative to the risk of having a non–methicillin-resistant *S. aureus* infection.[21] Similar to our study, Kiran et al. and Frazee et al. found the most common presentation to be abscesses (reported as furuncles in the article by Frazee et al.).[7,20] The incidence of culture-proven methicillin-resistant *S. aureus*–involved hand infections in this study was found to be 71.7 percent, which has increased from 61 percent over a 4-year period at the same institution, reported by the same authors in a retrospective review.[12] This finding was concerning enough to warrant immediate and premature cessation of this prospective trial by the institutional review board, as they deemed it unsafe and even unethical to administer empiric antibiotics not effective against methicillin-resistant *S. aureus* in the face of an incidence this high. Interestingly, although no clinical difference was found overall between the two groups, when the cefazolin patients who did not have methicillin-resistant *S. aureus*–positive cultures were excluded, the group who had methicillin-resistant *S. aureus* and received cefazolin had a higher mean cost of treatment compared with the vancomycin patients. This difference was not seen when their mean lengths of stay were compared, but this did trend toward significance. It is possible this may not have achieved statistical significance because of the underpowering of the study as a result of premature closure by the institutional review board, with only 42 of 100 patients enrolled.

Many publications, including those by Stacey et al.[22] and Kiran et al.,[20] provide algorithms for treating community-acquired methicillin-resistant *S. aureus*, which include assessing risk factors associated with methicillin-resistant *S. aureus* such as history of methicillin-resistant *S. aureus* infection/colonization, injection drug use, incarceration, human immunodeficiency virus, and others, and if there were no risk factors, to use traditional therapy (i.e., use of beta-lactams or cephalosporins). They give their low-risk hand infections a trial of non–methicillin-resistant *S. aureus* therapy. One result from our study is that we now treat all our surgical hand infections as "guilty of methicillin-resistant *Staphylococcus aureus*" until proven otherwise, for all comers (incarcerated patients were excluded from our study; thus, the high number cannot be attributed to them).

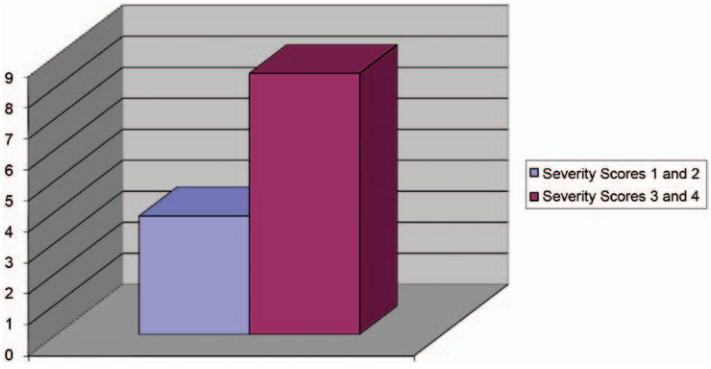

Fig. 7. Mean length of stay per severity score.

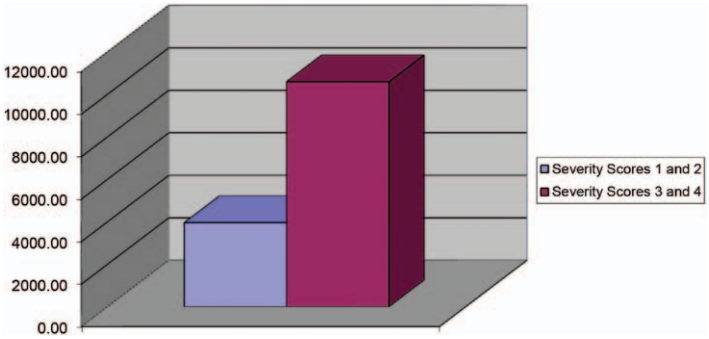

Fig. 8. Mean cost per severity score.

An admitted shortcoming of this study is the number of enrolled patients. It is possible that with an increased number of patients in each group, a statistically significant difference between the groups may have been detected. A power analysis conducted before the study estimated that approximately 50 patients would be needed in each group for reasonable statistical significance to be obtained. As mentioned above, the institutional review board prematurely closed our prospective study after opening the data set and determining an alarmingly high community-acquired methicillin-resistant *S. aureus* incidence of 72 percent. In addition, with additional patients may also have come added information on the incidence of methicillin-resistant *S. aureus*. It is likely that the incidence would be at least that reported in this study, if not higher—a fact that further underscores the conclusions drawn by the institutional review board. It is interesting to note that the costs of stay for methicillin-resistant *S. aureus*–positive patients who were assigned to the cefazolin group were statistically significantly higher. The comparison of length of stay did not reach statistical significance for the cefazolin arm patients, and costs of stay were no different for overall vancomycin versus cefazolin patients. This is likely a statistical anomaly, as these numbers trended toward significance, demonstrating that patients randomized to cefazolin would have likely had higher numbers in all categories had the study continued until the target sample size was achieved.

Another limitation of this study is the fact that the treatment team (residents and attending physicians) managing the patients was not blinded to the antibiotic being administered, despite the fact that the patients were randomized at the time of presentation. Considering the widely held belief that vancomycin is a stronger antibiotic, and that its effectiveness against methicillin-resistant *S. aureus* is much higher, there exists the possibility that a patient randomized to cefazolin would have been treated differently, and that they would have been considered at higher risk for reoperation, and thus may have received more attention, nursing interventions, and so forth, whereas vancomycin patients might have received care biased toward less clinical involvement. Although this cannot be confirmed or refuted, it remains a possible theoretical limitation of the study.

Admittedly, outpatient follow-up after discharge was suboptimal, as can be the case with this particular subpopulation of patients who present to our county hospital. Patients who came to our hand clinic were typically referred to occupational therapy. This cost was not factored into the analysis. This is a further weakness of the study, as it cannot be determined whether patients randomized to cefazolin versus vancomycin had any difference in long-term costs and functional outcomes.

Despite these limitations, one clear conclusion involves the utility of the hand infection severity score in predicting hospital cost and length of stay. Severity of hand infection was directly proportional to a more difficult hospital course, a longer hospital stay, and more expensive treatment regimen. This finding alone places the burden on the physician to aggressively treat the less severe infections to prevent conversion into a more severe score.

Although it may be tempting to conclude that early empiric antibiotic therapy before culture detection may be less important than standard operative débridement alone and culture-directed therapy, this conclusion cannot be drawn. The message in our data suggests that aggressive surgical débridement is likely more important than choice of empiric antibiotics in terms of outcomes (at least insofar as length of stay is concerned). There was no difference in clinical outcomes between patients randomized to vancomycin versus cefazolin, and the only statistically significant differences between these groups were costs and lengths of stay in methicillin-resistant *S. aureus*–positive patients. This further emphasizes the primary importance of surgical drainage in the treatment of hand

infections. However, based on these data, it must be understood that the cost of treatment may be decreased by the early, empiric administration of vancomycin. At this time, all patients admitted to the plastic surgery service at Parkland for hand infections are started on vancomycin to empirically treat for methicillin-resistant *S. aureus* given the proven high incidence of community-acquired methicillin-resistant *S. aureus* in the presenting subpopulation. Multi-institutional studies with larger numbers will be able to more clearly delineate the effects of empiric coverage for methicillin-resistant *S. aureus* in upper extremity soft-tissue infections.

CONCLUSIONS

This study adds to the literature outlining the growing incidence of methicillin-resistant *S. aureus* in the community hospital setting. In this study, the detected incidence of methicillin-resistant *S. aureus* of nearly 72 percent of all emergency room hand infections represents a significant increase at our institution over several years. Because of the premature closure of this prospective study, it is highly likely that the incidence is even higher than this. Patients randomized to cefazolin who ended up with methicillin-resistant *S. aureus*–positive cultures had higher mean costs of treatment compared with patients who were randomized to vancomycin. As expected, the more severe the infection, the heavier the cost incurred to both the patient and the hospital. Therefore, in addition to standard adequate operative débridement, early aggressive empiric therapy with coverage for methicillin-resistant *S. aureus* is warranted in treatment of hand infections.

Jeffrey E. Janis, M.D.
Department of Plastic Surgery
The Ohio State University Medical Center
915 Olentangy River Road, Suite 2100
Columbus, Ohio 43212
jeffrey.janis@OSUMC.edu

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