### Instructions

1. Review the stated learning objectives at the beginning of the CME article and determine if these objectives match your individual learning needs.
2. Read the article carefully. Do not neglect the tables and other illustrative materials, as they have been selected to enhance your knowledge and understanding.
3. The following quiz questions have been designed to provide a useful link between the CME article in the issue and your everyday practice. Read each question, choose the correct answer, and record your answer on the CME REGISTRATION FORM at the end of the quiz.
4. Type or print your full name and address and your date of birth in the space provided on the CME Registration Form.
5. Indicate the total time spent on the activity (reading article and completing quiz). Forms and quizzes cannot be processed if this section is incomplete. All participants are required by the accreditation agency to attest to the time spent completing the activity.
6. Complete the Evaluation portion of the CME Registration Form. Forms and quizzes cannot be processed if the Evaluation portion is incomplete. The Evaluation portion of the CME Registration Form will be separated from the quiz upon receipt at ORTHOPEDICS. Your evaluation of this activity will in no way affect the scoring of your quiz.
7. Send the completed form, with your $15 payment (check or money order in US dollars drawn on a US bank, or credit card information) to: ORTHOPEDICS CME Quiz, PO Box 36, Thorofare, NJ 08086. OR take the quiz on-line. Visit www.ORTHOSuperSite.com for details.
8. Your answers will be graded, and you will be advised whether you have passed or failed. Unanswered questions will be considered incorrect. A score of at least 80% is required to pass. If a passing score is achieved, Vindico Medical Education will issue an AMA PRA Category 1™ certificate within 4-6 weeks.
9. Be sure to mail the CME Registration Form on or before the deadline listed. After that date, the quiz will close. CME Registration Forms received after the date listed will not be processed.

### CME ACCREDITATION

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Vindico Medical Education and ORTHOPEDICS. Vindico Medical Education is accredited by the ACCME to provide continuing medical education for physicians. Vindico Medical Education designates this Journal-based CME activity for a maximum of 1 AMA PRA Category 1™ Credit. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is primarily targeted to orthopedic surgeons, hand surgeons, head and neck surgeons, trauma surgeons, physical medicine specialists, and rheumatologists. There is no specific background requirement for participants taking this activity.

### FULL DISCLOSURE POLICY

In accordance with the Accreditation Council for Continuing Medical Education’s Standards for Commercial Support, all CME providers are required to disclose to the activity audience their relevant financial relationships with the planners, teachers, and authors involved in the development of CME content. An individual has a relevant financial relationship if he or she has a financial relationship in any amount occurring in the last 12 months with a commercial interest whose products or services are discussed in the CME activity content over which the individual has control.

Dr. Saveli, Belknap, Morgan, and Price have no relevant financial relationships to disclose. Dr. D’Ambrosia, Editor-in-Chief, has no relevant financial relationships to disclose. The staff of ORTHOPEDICS have no relevant financial relationships to disclose.

### UNLABELED AND INVESTIGATIONAL USAGE

The audience is advised that this continuing medical education activity may contain references to unlabeled uses of FDA-approved products or to products not approved by the FDA for use in the United States. The faculty members have been made aware of their obligation to disclose such usage.

---

### Review Article

**The Role of Prophylactic Antibiotics in Open Fractures in an Era of Community-acquired Methicillin-resistant Staphylococcus aureus**

**CARLA C. SAVELI, MD; ROBERT W. BELKNAP, MD; STEVEN J. MORGAN, MD; CONNIE S. PRICE, MD**

#### Educational Objectives

As a result of reading this article, physicians should be able to:

1. Recognize and critically examine the supporting evidence for the current recommendations on antibiotic prophylaxis in open fractures.
2. Discuss the evidence behind the appropriate timing for administration and duration of prophylactic antibiotics in open fractures.
3. Describe the changing epidemiology of *Staphylococcus aureus* and increasing rates of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization in trauma patients.
4. Identify the implications for both the patient and the healthcare system of MRSA surgical site infections after open fractures.

#### Abstract

Infection is a feared complication and a common cause of loss of function following open fractures. Despite the evidence supporting the administration of prophylactic antibiotics after open fractures, data demonstrating the optimal regimen is lacking. We reviewed the data supporting the current prophylaxis recommendations and the changing epidemiology of *Staphylococcus aureus*, the most common cause of surgical site infection in patients with open fractures. Although widespread emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) has been described in both hospital and community settings, to date, no studies have addressed the need for prophylaxis.

---

Drs Saveli is from University of Colorado, Aurora, and Drs Belknap, Morgan, and Price are from Denver Health Medical Center, Denver, Colorado.

The material presented in any Vindico Medical Education continuing education activity does not necessarily reflect the views and opinions of ORTHOPEDICS or Vindico Medical Education. Neither ORTHOPEDICS nor Vindico Medical Education nor the authors endorse or recommend any techniques, commercial products, or manufacturers. The authors may discuss the use of materials and/or products that have not yet been approved by the US Food and Drug Administration. All readers and continuing education participants should verify all information before treating patients or using any product.

Correspondence should be addressed to: Carla C. Saveli, MD, University of Colorado Denver Medicine, Infectious Diseases, 12700 E 19th Ave B-168, Aurora, CO 80045 (carla.saveli@ucdenver.edu).

doi: 10.3928/01477447-20110627-25
against MRSA in patients with open fractures. Until well-designed randomized trials are conducted, we recommend that providers consider selecting antibiotics active against MRSA for open fracture prophylaxis based on the local prevalence of MRSA carriage and individualized risk factors.

Open fractures are characterized by soft tissue disruption that results in communication of the fracture site with the outside environment. Open fracture wounds are classified as class III or contaminated, as documented by Gustilo and Anderson who reported a positive bacterial tissue culture in 70.3% of 158 open fracture wounds. The reported wound infection rates after open fractures in the literature range broadly and depend on the severity of the injury. According to the Gustilo classification, the risk of infection after open fracture ranges from 0% to 2% for type I fractures, 2% to 15% for type II fractures, and 5% to 50% for type III fractures.

Restoration of function through optimal healing is the main goal when treating open fractures and prevention of infection by the use of antibiotic prophylaxis and wound debridement are critical to achieving this goal. The benefit of antibiotic prophylaxis in this setting has long been established. The regimen of prophylaxis should not be directed at all organisms isolated from a contaminated fracture site; rather it should be directed against the most relevant pathogens causing surgical site infection. Thus, the purpose of this review is to analyze the evidence behind the current recommendations for antibiotic prophylaxis in the management of open fractures and the changing epidemiology of Staphylococcus aureus, the most common cause of surgical site infection after open fractures.

**DATA SOURCES**

We performed a computerized bibliographic search using the databases Medline from 1950 to 2009 and Embase from 1980 to 2009 for English-language studies. We searched the terms: prospective, randomized, prophylactic antibiotic, fracture and/or orthopaedic to collect studies on antibiotic prophylaxis in open fractures. The terms: Staphylococcus aureus, methicillin-resistant Staphylococcus aureus (MRSA) colonization, prevalence, fracture, orthopedic and/or trauma were used to collect studies on the epidemiology of S aureus in trauma patients. We also reviewed the reference list of relevant trials retrieved by our electronic search.

We used the United States Preventive Services Task Force to stratify the quality of evidence. For the purpose of this review, 7 studies eligible as Level-I evidence were analyzed for antibiotic selection, timing and duration for prophylaxis in open fractures (Table). Studies with Level I and II evidence were selected for the epidemiology of S aureus in trauma patients. Thirteen articles were reviewed and referred to as evidence for the emergence of MRSA in orthopedic trauma patients.

**DATA SUPPORTING CURRENT PROPHYLAXIS RECOMMENDATIONS**

**Antibiotic Selection**

In 1974, Patzakis et al demonstrated a reduction of infections in patients with open fracture wounds who received prophylactic antibiotics. Cephalothin, a first generation antibiotic, was demonstrated to be superior to both no antibiotics and to a regimen of penicillin and streptomycin. The superiority of cephalothin was attributed to its activity against S aureus, the organism most often implicated as a cause of infection in open fractures, and generally resistant to penicillin and streptomycin. Although the penicillin and streptomycin regimen had broader coverage against gram negative and anaerobes when compared to cephalothin, the dual regimen did not differ significantly in preventing infections when compared to the placebo group. Thus the authors concluded that “antibiotics expected to be effective against coagulase-positive S aureus should be selected for prophylactic therapy of open fractures caused by direct trauma.”

In agreement with the findings of Patzakis et al, two randomized, controlled trials corroborate the benefit of prophylactic antibiotics directed against S aureus in the management of open fractures. Bergman, in 1982, demonstrated a significant decrease in both superficial and deep wound infection in open fractures with severe soft tissue injury with the administration of perioperative dicloxacillin compared with placebo. Subsequently, a similar trial by Braun et al confirmed the benefit of using prophylactic dicloxacillin against placebo for prevention of infection in open fracture wounds. A consistent finding of these studies was the need for prophylaxis with agents that have activity against gram positive organisms and specifically S aureus, which accounts for 50% of surgical site infections after open fractures. It should be noted that both dicloxacillin and cloxacillin have a narrow spectrum of activity directed exclusively at S aureus and some species of aerobic and anaerobic streptococci, and with no activity against gram negative organisms or obligate anaerobes.

Despite the evidence supporting systemic prophylactic antibiotics after open fractures active against S aureus, data demonstrating the optimal antistaphylococcal regimen is lacking. The current quality standard for the management of open fractures includes the administration of parenteral antibiotic prophylaxis with an effective regimen consisting of a first generation cephalosporin, usually cefazolin. This is a class IA recommendation implying that this intervention is effective with evidence derived from multiple randomized clinical trials. However, since these studies were conducted, the epidemiology of gram positive organisms causing surgical site infection has changed. All these landmark studies were accomplished before the widespread emergence
of MRSA as a cause of infection in patients with open fractures.\textsuperscript{8,10} Methicillin resistance among \textit{S. aureus} is now widespread in both hospital and community settings.\textsuperscript{10,11} Yet, guidelines still promote antibiotics that cover a decreasing proportion of \textit{S. aureus}, those that remain susceptible to methicillin.\textsuperscript{7,8}

Conversely, the role of gram negative rods and the need for prophylaxis against these organisms has not been established. Bergman described gram negative infections as “infrequent and healed without supplementary treatment with systemic antibiotics.”\textsuperscript{15} Two placebo-controlled trials reported a rate of gram negative surgical site infection between 9.6 to 14.2, most of them caused by pseudomonas species that are not within cefazolin’s spectrum of activity.\textsuperscript{4,5} In a 1999 double-blind controlled trial by Carsenti-Etesse et al, 616 patients with open tibial fracture requiring open reduction and internal fixation were randomized to receive pefloxacin versus cefazolin after their fracture and assessed for surgical site infection within 3 months.\textsuperscript{12} Although pefloxacin has activity against pseudomonas species and overall a broader spectrum of gram negative coverage than cefazolin, there was no difference in surgical site infection rates between the 2 groups (7% vs 8%, respectively, \(P = .51\)). Finally, it should be noted that vancomycin, an antibiotic with no activity against gram negative rods, is recommended for the antibiotic prophylaxis of open fractures in beta-lactam allergic patients without the addition of a second agent with gram negative activity.\textsuperscript{8}

The most recent evidence-based systematic review to define the Surgical Infections Society guidelines on prophylactic antibiotic use in open fractures concluded that there is insufficient data on gram negative prophylaxis to justify such coverage.\textsuperscript{7} Despite the lack of evidence, a recent survey answered by 74 program directors from academic orthopedic resi-
of healthy people are carriers of
for prevention of fracture site infections. Therefore, the benefits of adding gram negative prophylaxis in specific fracture types and its impact on antibiotics resistance remain to be determined by future investigations.

Timing and Duration of Prophylactic Antibiotics

The goal of antibiotic prophylaxis in open fractures is to achieve adequate tissue levels as soon as possible following the injury. Patzakis and Wilkins demonstrated a clear benefit if antibiotics are given within 3 hours after the injury with a rate of infection of 4.7% compared with a rate of 7.4% if antibiotics were delayed for >3 hours.

Conversely, the duration of prophylactic treatment is not well established and remains a topic of discussion. Many authors advocate the use of prophylaxis for 3 days. However, a prospective, double-blind, randomized controlled trial showed that antibiotics administered for 24 hours were not inferior to a prolonged course in specifi c fracture types and its impact on morbidity and restricted therapeutic options.

In addition, the duration of prophylactic antibiotic regimens is directly related to the probability of developing resistant microorganisms. As a result, the current guidelines recommend the administration of prophylactic antibiotics within 3 hours of the injury until 24 hours after the surgical intervention. Additional prophylaxis for 24 hours is recommended for subsequent interventions in the same surgical area.

Emergence of MRSA as a Cause of Infection After Open Fractures

Previous studies have shown that 37% of healthy people are carriers of S aureus on their anterior nares and skin, and this carriage predisposes them to a higher risk of S aureus surgical site infection. Shukla et al screened for MRSA colonization 2473 adult patients admitted to a trauma ward in England. They found that the rate of MRSA surgical site infection was significantly higher for MRSA carriers compared to those not colonized (8.8% vs 2.3%, P < .001). They concluded that MRSA carriers have a 2.5-times higher risk than that of the normal population of developing postoperative MRSA surgical site infection.

Beginning in 2003, major cities in the United States have experienced increasing rates of MRSA colonization and infection originating in the community. This “community-acquired” strain, frequent in patients without the classic risk factors, has similar virulence, resistance, and limited treatment options as those originating in the hospital. Reported MRSA colonization rates in trauma patients have been higher than expected (10.44%) compared to the prevalence in general orthopedic patients (4%-5.6%). This finding parallels the increase in MRSA surgical site infections after fracture fixation in both elective and acute trauma patients representing a challenge to clinicians knowing its associated increased morbidity and restricted therapeutic options.

Carsenti-Etesse et al first described the emergence of hospital-acquired MRSA as well as methicillin-resistant coagulase negative staphylococci as a cause of infection after open fractures and the concerns for broader prophylactic coverage against these organisms. They evaluated the bacteriology of infections in open leg fracture wounds and confirmed that S aureus accounts for the majority (37%) of these, with almost a third of them caused by MRSA.

Recently, in an effort to determine the contemporary microbiology of surgical site infection in open fractures, Johnson et al characterized the infections seen in conjunction with combat-associated type III tibial fractures. In this case series, 35 patients wounded in Iraq or Afghanistan who received prophylactic cefazolin and surgical debridement for an open fracture were analyzed. In all, 13 patients developed infection and delayed union. Surgical cultures taken from the delayed union site revealed S aureus in 69% of the cases (9 of 13 patients) with more than a third (4 of 13) due to MRSA. Although this study does not allow the authors to make recommendations on antibiotic prophylaxis, they emphasize the need for further investigations on this topic.

In an attempt to address the increasing prevalence of MRSA surgical site infection, a randomized controlled trial performed in elective orthopedic patients concluded that glycopeptides such as teicoplanin ensure adequate surgical prophylaxis comparable to cefazolin in this setting. Additionally, a quasi-experimental cohort study performed in Europe demonstrated significantly reduced rates of MRSA surgical site infection (2.73 vs 0.19, P < .005) in elective orthopedic patients by adding high dose teicoplanin to the standard antibiotic prophylaxis regimen. Most recently in 2008, the Society for Healthcare Epidemiology of America in collaboration with Infectious Diseases Society of America published their recommendations to prevent surgical site infection in acute care hospitals. They highlighted the importance of prophylaxis against MRSA in specific clinical circumstances and the need for prospective trials looking at the addition of a glycopeptide to standard antibiotic prophylaxis.

Once infection with MRSA occurs, cure is difficult. Staphylococcus aureus have a propensity to cause bone and joint infections and seem to have the ability to persist in a latent state and cause recrudescence infections after decades. This organism expresses several factors that compromise the effectiveness of neutrophils and macrophages, the first line of defense against infections. In addition, S aureus can survive in phagosomes, and express polysaccharides and proteins that inhibit opsonization by antibodies and complement. These characteristics make treatment of even methicillin susceptible
strains of \textit{S aureus} challenging, and the added factor of methicillin resistance poses even more challenges due to limited and perhaps suboptimal treatment options.

Treatment involves prolonged courses of antibiotic with activity against MRSA; however, the organisms cannot be eradicated completely with this regimen until radical debridement, including hardware removal, is performed.\textsuperscript{32} This may not be possible in many cases until fracture union is complete leading to either infection relapses or chronic suppression with prolonged courses of oral antibiotics.

Johnson and Johnston\textsuperscript{9} reported a case series of 38 patients with MRSA infection related to their orthopedic intervention site during a hospital outbreak. The majority (84\%) had surgical debridement and stabilization of a fracture with subsequent surgical site infection. They found that orthopedic infections due to MRSA carry extreme morbidity as a result of prolonged hospitalization, increased number of surgical procedures per patient, higher amputation rates, loss of musculoskeletal function, and extreme cost for both medical care and time lost from productive employment. In addition, studies assessing adverse outcomes associated with MRSA surgical site infections compared to those with methicillin sensitive strains found greater 90-day mortality rate, 1.19-fold increase in hospital costs,\textsuperscript{33} and increased mortality at 12 months.\textsuperscript{20} Considering the detrimental consequences of MRSA in musculoskeletal surgical site infections, the local prevalence of MRSA and specific risk factors are likely to be important variables in the choice of a prophylactic strategy in open fractures.

**Conclusion**

Antibiotic selection for prophylaxis in open fractures should be influenced by organism most often implicated as a cause of infection and by the relative cost and availability of the agents. \textit{Staphylococcus aureus} is the most common organism causing surgical site infection in this setting and in agreement with previous studies it should be the main target of prophylaxis. However, the epidemiology of this organism has changed and methicillin sensitive strains are being replaced by those methicillin resistant. In addition, MRSA, thought to be a hospital-acquired organism, is now originating in the community. Despite the fact that trauma patients come from the community and do not have the usual risk factors for MRSA acquisition, the number of MRSA infection in this population is dramatically increasing leading to significant morbidity and higher hospital costs.

Considering the increasing rates of MRSA infection after open fractures, a large multicenter study should be initiated to determine the epidemiology of \textit{S aureus} in trauma patients and whether targeted MRSA prophylaxis should be recommended for such patients. In the meantime, we recommend that providers consider selecting antibiotics active against MRSA for open fracture prophylaxis based on the local prevalence of MRSA carriage, surgical site infection rates and individualized risk factors.

**References**


