A Prospective Randomized Trial to Assess Oral Versus Intravenous Antibiotics for the Treatment of Postoperative Wound Infection After Extremity Fractures (POvIV Study)

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Summary: Patients surgically treated for infection after extremity fractures are typically discharged with a 6- to 12-week antibiotic regimen. Intravenous (IV) antibiotics are associated with significant cost and potential complications of deep vein thrombosis, line clotting, and sepsis. Many of the pathogens that cause musculoskeletal infection have both oral (PO) and IV antibiotic options with adequate bioavailability and antibacterial effect, yet IV antibiotics remain the standard of care absent evidence that PO options are clinically as efficacious. The POvIV study is a prospective, multicenter, randomized trial to compare PO with IV antibiotic therapy in patients with postoperative wound infections after extremity fractures. Patients between the ages of 18 and 84 who have a culture-positive surgical site infection after internal fixation for fracture repair or arthrodesis are approached for this study, and if they provide consent, are randomly assigned to receive either PO or IV antibiotics. Antibiotic selection is based on culture and sensitivity results. Randomization determines the route of administration. Patients are followed for 1 year after study enrollment. This study will be the largest prospective randomized trial to evaluate the safety and effectiveness of PO antibiotic use for treatment of postoperative wound infections. Results will inform clinician decisions on antibiotic delivery in patients with postoperative wound infections.

Key Words: IV, PO, antibiotics, surgical site infection, wound infection, extremity fractures, joint fusions, fixation

(*J Orthop Trauma* 2017;31:S32–S38)

BACKGROUND AND RATIONALE

Infection is a common complication after fracture surgery and particularly when there is severe soft-tissue injury associated with open fractures such as those in combat-related injuries.[1] Factors that raise the risk of postoperative infections include open wounds, gross contamination, loss of soft tissue, poor vascularity to tissues, multiple operations, associated injuries, immune compromise, prolonged hospital stays with exposure to nosocomial bacteria, and the presence of a metal implant.[2–5] The development of an infection prolongs recovery and increases the risk of nonunion, amputation even sepsis, and death. In civilian extremity fractures, the Lower Extremity Assessment Project showed that osteomyelitis has a significant negative impact on the final functional outcome of the patient.[6,7] Similarly, in the military setting, approximately 55% of casualties from the Iraq and Afghanistan conflicts sustained major extremity trauma, typically from blast injuries and up to 15% of the resulting open fractures develop osteomyelitis.[8,9] The treatment of infections and associated complications prolongs hospitalizations, negatively impacts long-term outcomes, and increases medical costs.

Drainage, debridement, and dead space obliteration coupled with a prolonged course of antibiotics is the standard of care for deep postoperative wound infections in orthopaedic trauma.[10–12] Clinicians are currently required to make 2 critical decisions when presented with acute, deep wound infections: implant retention versus removal and the type and duration of antibiotic to be used.

The first major question of implant retention versus removal is beyond the scope of this study, although a few studies have suggested that implants can be retained and infection suppressed until fracture union.[13,14] The second major question relates to antibiotic therapy. Current treatment

Accepted for publication January 13, 2017.

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The authors report no conflict of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jorthotrauma.com).

ClinicalTrials.gov No. NCT01714596.

Department of Defense Contract No.: W81XWH-10-2-0133.

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DOI: 10.1097/BOT.0000000000000802

regimens practiced throughout North America and Europe require patients with postoperative infections to receive prolonged intravenous (IV) antibiotic therapy after surgical debridement. Prolonged IV therapy is associated with a substantial risk of line sepsis, tip occlusion, and vein thrombosis. In addition, parenteral antibiotic therapy is expensive and is not available to all patients because of the cost, history of IV drug abuse, or the potential for noncompliance with treatment recommendations.

Few data are available on infection after fracture fixation, but the total joint literature provides a reasonable comparison. Over the last decade, several studies have demonstrated the efficacy of the oral (PO) fluoroquinolones, ciprofloxacin, and ofloxacin for the treatment of serious bone and joint infections.[5] In addition, the PO antibiotic linezolid has recently been introduced. Linezolid is active against many of the so-called resistant organisms, including methicillin-resistant staphylococcus aureus and enterococcus. It is evident that there are now PO antibiotics that cover a wide range of typical pathogens encountered in orthopaedics and that have acceptable penetration into bone and joint fluid.[13,15–19]

There is also an extensive literature describing the successful use of PO antibiotic therapy for the management of adult and pediatric osteomyelitis.[15,17,18,20–23] In a controlled clinical trial, Mader et al[5] compared treatment with PO ciprofloxacin to IV nafcillin, clindamycin, and gentamicin in adult patients with chronic osteomyelitis. After 30 months of follow-up, the infection was eradicated in 11 of 14 patients (70%) treated with ciprofloxacin compared with 10 of 12 (83%) who had IV therapy. In another prospective, randomized study, 31 patients with osteomyelitis received PO ciprofloxacin (750 mg twice daily) and 28 were treated with IV cephalosporin or nafcillin–aminoglycoside combination.[24] The clinical success rate was 77% for the ciprofloxacin group compared with 79% for the IV group. Adverse drug reactions occurred in only 3% of the patients who received ciprofloxacin compared with 14% of the patients treated with IV antibiotics.[24] Swiontkowski et al[23] showed in a case series that 6 weeks of PO antibiotic therapy with either trimethoprim–sulfamethoxazole or ciprofloxacin after thorough surgical debridement was successful in 80 of 93 cases (91%). Nearly a third of these patients had concomitant internal fixation of persistent bone defects. PO antibiotic therapy is now considered appropriate for most cases of osteomyelitis caused by sensitive organisms.[15,22] As the study by Swiontkowski et al[23] shows, PO antibiotic therapy can also be successful in implant-related musculoskeletal infections, when combined with appropriate surgical treatment.

Several studies have reported that cost reductions are 2- to 10-fold when PO antibiotic therapy is used as compared to IV therapy.[15] The cost of IV drug therapy includes the costs of placing and maintaining long-term venous access and the cost of a medication pump or visiting nurse. These costs can range from $3500 to over $10,000 for a 6-week course of IV home antibiotics.[25] If one considers the additional cost of outpatient IV antibiotic delivery, the cost differential between PO and IV antibiotic use is even more profound. The total cost for outpatient IV antibiotic administration can range from $70 to $246 per day compared with $7 per day for PO fluoroquinolones. The cost of Linezolid, as a PO antibiotic effective against methicillin-resistant staphylococcus aureus (MRSA), is significant and can be $200–2000 for a 4 week course, although even this amount may compare favorably with IV therapy for a similar period.[26]

Despite the potential of PO antibiotics, there is currently no level I data supporting their use in this setting. Given the existence of important research gaps in this topic and the potential for both cost reductions and the avoidance of adverse events, it is essential to develop high-level evidence to inform clinician choices and potentially inform practice changes. The main aim of the POvIV study is to evaluate the effect of treatment of postoperative wound infection in bones after fracture fixation or joint fusion with either operative debridement or PO antibiotic treatment for 6 weeks or operative debridement and IV antibiotics for 6 weeks. The primary hypothesis is that the mean number of study injury–related surgical interventions by 1 year in the PO group will be noninferior to the rate in the IV group. Furthermore, it is hypothesized that the rates of treatment failure and rehospitalization for complications, infection, nonunion, and amputation, as well as adherence and patient satisfaction with treatment in the PO group will be noninferior to the IV group. Finally, it is expected per patient treatment costs at 1 year will be lower in the PO group than in the IV group.

METHODS: TRIAL DESIGN AND PARTICIPANT SELECTION

Trial Design

The POvIV study is a prospective, multicenter, randomized trial to compare PO with IV antibiotic therapy in patients with postoperative wound infections after extremity fractures. Twenty-four trauma centers within the Major Extremity Trauma Research Consortium (METRC) (listed at the end of this article) are participating in this study.[27] The study protocol, including the written informed consent form, was approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board (IRB) (location of the METRC Coordinating Center), the Department of Defense Human Research Protection Office (study sponsor), and the local IRB at each participating center. In addition, each site was required to obtain Department of Defense Human Research Protection Office approval of the local IRB documents and certification by the METRC Coordinating Center (MCC) to ensure proper training in study procedures and data collection beforethe initiation of the study.

Participant Selection

Patients between the ages of 18 and 84 who have undergone fracture repair or arthrodesis with internal fixation and developed a culture-positive deep surgical site infection (SSI) are approached for this study. Deep SSI is defined based

TABLE 1. POvIV Study Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Patients aged 18–84 y with any fractures of any bone at or proximal to and including the tarsal/metatarsal joint (Lisfranc) or proximal to the carpal joints (includes distal radius fractures), excluding the spine, treated with any type of internal fixation, or	1. Patients who have a high risk of amputation of the study limb based on opinion of the initial managing physician.
2. Patients undergoing fusion of any bone at or proximal to and including the subtalar joint or radial carpal joint (excluding the spine) that develop a postoperative wound infection at any time.	2. Patients undergoing treatment with any other investigational therapy within the month preceding implantation or planned within the 12 mo after implantation.
3. Patients diagnosed with a wound infection of the study injury, defined as deep culture positive after operative debridement.	3. Patients with history of chronic infection at the site of study injury, defined as patients with chronic osteomyelitis identified by radiographic erosion or sequestrum or patients with more than one instance of surgical treatment of infection and approximately a 6-wk course of antibiotics.
4. Patients who are English or Spanish competent.	4. Patients with pathological fractures or a known history of Paget disease.
5. Patients with bacteria susceptible to both PO and IV antibiotics.	5. Patients for whom the definitive treatment of the study injury was an external fixator.
6. Patients able to be treated for their infection at the METRC facility for at least 12 mo after definitive surgical procedure.	6. Patients with MRSA infection who are currently on selective serotonin reuptake inhibitor (SSRI) medication (eg, Zoloft, Prozac, and Celexa).
7. Patients may have multiple study eligible injuries.	7. Patients with cultures positive in thio only; (8) patients who are incarcerated or who have unstable housing situations because of concerns regarding ability to receive home care, monitoring phone calls, and maintain follow-up.
8. Patients may have had temporary external fixation before definitive fixation.	8. Patients or designated proxies who are unwilling to provide consent.
9. Patient is able to obtain study medications.	9. Patients with a history of IV drug use who in the investigator's opinion are unsuitable candidates for IV therapy.
10. Patient may be pregnant at the time of screening.	10. Patients likely to have severe problems maintaining follow-up, including patients diagnosed with severe psychiatric conditions and patients who live too far outside the hospital's catchment area.
11. Patients may have received antibiotics before operative wound debridement.	11. Patients with traumatic brain injury or who are intellectually challenged and who lack adequate family support to ensure adherence to the protocol.
	12. Patients unable to swallow PO medications or without an adequately functioning GI tract.
	13. Patients who, based on the clinical judgment of the treating clinician, are not equally suited for treatment with either PO or IV antibiotics (ie, those for whom there is a clinical treatment preference).

on the CDC criteria and involves only patients whose infection is treated operatively.[28] Patients who only have superficial SSI, which are defined as those treated without surgery, do not meet inclusion criteria. Eligible patients must have had internal fixation at one time to treat the fracture or achieve fusion but do not need to have the implants still in place at the time of study enrollment. Patients with fractures treated only with external fixation, and no implants below the skin, are not eligible. Patients with osteomyelitis (defined as radiographic evidence of bone erosion or sequestra in the setting of a deep infection) are excluded from the study. Infection that extended to bone and internal fixation but not associated with findings of radiographic erosion and positive bone cultures are considered a distinct entity from acute or chronic osteomyelitis, which includes one or both of those findings.

After providing informed consent and meeting all eligibility criteria, patients are randomly assigned to receive either PO or IV antibiotics. Randomization is performed centrally, using the METRC web-based, distributed data collection system. The randomization scheme assigns patients in a 1:1 ratio in randomly permuted blocks stratified by the clinical center. The block size was hidden from sites and varied by site based on volume. Patients are followed for 1 year after initial infection hospitalization discharge.

Patients meeting all criteria who decline participation in the randomized trial may be considered for an observational arm. Participation in the observational arm is offered 24 hours after a patient's refusal to participate in the randomized controlled trial (RCT). Enrollment in the observational arm is also considered for patients who must be prescribed PO or IV based on institutional policy or because of insurance coverage that does not include coverage for a potential mode of study medication administration. Enrollment in the observational arm is not considered based on a clinician's preference for IV or PO medications. Detailed inclusion and exclusion criteria are described in Table 1.

METRC uses a comprehensive informed consent process for all of its studies that involves the treating clinicians, the clinical site research coordinators, and educational resources for patients and family members to facilitate informed decision making about participation (see **Figure, Supplemental Digital Content 1**, http://links.lww.com/BOT/A859).

Sample Size

For the primary outcome of surgical procedures, based on previous data, it will be assumed that the distribution will follow a zero-inflated Poisson model with mean number of surgical procedures of 2.17 and a variance of 4.16. PO antibiotics will be considered to be noninferior to IV antibiotics, if the difference in mean number of additional procedures within 1 year for PO versus IV antibiotic therapy is less than or equal to 0.67. Slightly more procedures (on

average) for PO as a tradeoff for the convenience/cost will be tolerated. The assessment of noninferiority proceeds by evaluating whether the upper limit of an appropriately sized confidence interval for the difference in means (PO minus IV) is less than or equal to 0.67. An interim analysis will be conducted when 50% of patients have been followed for at least 1 year. The width of the confidence intervals will be set to control the overall type I error (probability of accepting equivalence when it is false) of 5%. The sample size is set so that the power (probability of accepting noninferiority when it is true) is 80%. The O'Brien–Fleming alpha-spending function will be used to construct the width of the confidence intervals. Assuming that the first interim analysis is conducted after 50% of the patients have been followed for 1 year, a 99.44% 1-sided confidence interval at the first interim analysis and a 95.18% 1-sided confidence interval at the final analysis will be constructed. The data will be analyzed using a 2-sample *t*-based confidence interval and 10% missing data. These assumptions require enrollment of approximately 132 patients per randomized arm.

Intervention

On admission and until randomization, patients are treated with broad-spectrum IV antibiotics while awaiting surgical culture and sensitivity results per the local surgeon and infectious disease team. After randomization, the infectious disease team, in consultation with the surgeon, determines if the patient can be treated using either PO or IV antibiotics based on bacterial sensitivity results from cultures. Management of study patients (in both arms) including clinical, laboratory, and radiographic assessments does not differ from standard of care.

All patients receive weekly phone calls from the Vanderbilt Call Center for the first 6 weeks of the prescribed antibiotic regimen. Patients randomized to the PO arm are also monitored using an adherence cap. The Medication Event Monitoring Systems (MEMS; MWV Switzerland Ltd) adherence cap automatically compiles drug dosing history data by electronically recording the date and time of each opening of the medication container. The patient is instructed to open the bottle with the MEMS cap when it is time to take the medication, to remove the medication, promptly close the bottle, and ingest the prescribed dose. Once the prescribed course of antibiotics has been completed, the patient returns the cap to the study coordinator at the research site. The coordinator then sends the cap to the METRC Coordinating Center by mail where the dosing history is downloaded, using a cap reader and transferred to a secured centralized database.

Protocol Changes

Several modifications were made to the protocol when the study was conducted. First, changes to the inclusion criteria were made to include additional types of fractures and to include arthrodesis of major joints of the extremities. Inclusion criteria were also expanded to include fixation with intramedullary nails, whereas initially only plate fixation was included. Third, to address concerns regarding low participation/consent rates, the observational arm was added for reasons cited above. Third, the inclusion/exclusion criteria were amended to exclude only patients with a history of chronic osteomyelitis at the injury site before new fracture versus initial criteria that included only those whose infection developed within 6 weeks of initial injury. Finally, the adherence cap provider was changed from Vitality Glowcap to MEMS cap as Vitality discontinued support for remote adherence monitoring through cellular networks.

METHODS: DATA COLLECTION AND ENDPOINTS

Frequency and Duration of Follow-up

Patients return for standard follow-up visits at 2, 6, 12, 26, and 52 weeks after discharge from the study infection hospitalization. Data are also captured for visits occurring outside the study visit schedule when it involves hospitalizations or complications. Data captured at each visit are summarized in **Supplemental Digital Content 2** (see **Table**, http://links.lww.com/BOT/A862).

Primary Endpoint

The primary endpoint for this study is the number of surgical interventions on the study injury within 1 year, excluding the initial surgical debridement(s) leading to study enrollment.

Secondary Endpoint

Treatment Failure

Treatment failure is defined as the occurrence of at least one of the following: (1) wound problems requiring additional surgery more than 2 weeks after the last of the initial debridements for infection and randomization; (2) culture-positive recurrence of infection before bony union as evidenced by persistently elevated or progressively increasing erythrocyte sedimentation rate and C-reactive protein in the context of recurrent wound drainage and no history of inflammatory arthritis; (3) among study subjects with plate fixation, progressive radiographic loosening of the fixation as evidenced by progressive radiolucent line development, implant breakage, or loss of reduction of the fracture; (4) infection-induced joint erosion that requires arthrodesis or amputation to eradicate infection; (5) adverse reaction to any of the antibiotics that requires a change from one form of administration to another; and (6) development of an infection with a new organism, defined as an organism not identified at the time of diagnosis of previous infection.

Rehospitalization for Complications

Rehospitalization for complications are defined as any readmission to the hospital for treatment of the deep wound infection associated with the index fracture fixation for a defined set of complications. The list of complications includes amputation, infection, flap failure, osteomyelitis, and nonunion with positive culture or fixation failure as previously defined; any complication of IV access including, but not limited to central line–associated blood stream infection or line sepsis, deep vein thrombosis in same

extremity as IV access, pneumothorax, or line change due to malfunction; admission due to antibiotic side effects such as organ failure or insufficiency, hypersensitivity, or bone marrow suppression; mechanical failure of implant requiring revision fixation or amputation proximal to the level of injury.

Nonunion

Radiographic union is assessed by a blinded panel of orthopaedic surgeons at 6 months. Clinical union is assessed by the treating surgeon and is defined as pain free, full weight bearing, and no tenderness to palpation at the fracture site. The fracture is considered to be a clinical success (ie, healed), when radiographic union is confirmed and both clinical parameters listed above for union are met.

Amputation

Amputation is defined as surgical procedure to remove part of an extremity proximal to the site of the study infection because of persistent infection or nonunion.

Health Care Costs

Medical resource utilization and direct costs of medical care received by study patients during the 1-year follow-up period begins on discharge from the index study hospitalization. Costs include those associated with outpatient clinic visits, home health visits, medications, subsequent hospital readmissions, and other types of medical care as identified over the course of the study.

Patient Adherence

Adherence to medication is reported by patients in both arms through weekly telephone interviews and through analysis of MEMS cap data for patients in the PO arm.

Patient Satisfaction With Treatment

Patient satisfaction with treatment is measured using the Short Form Patient Satisfaction Questionnaire (PSQ-18)[29] at the 12-month follow-up visit.

Monitoring and Quality Assurance

An independent Data Safety Monitoring Board reviews study progress and reported complications and adverse events twice a year. The chair of the Data Safety Monitoring Board serves as the medical monitor and reviews serious adverse events as reported in real-time (see **Figure, Supplemental Digital Content 3**, http://links.lww.com/BOT/A860).

METHODS: DATA MANAGEMENT AND ANALYSIS

Data Management

Data are collected by site research coordinators and clinical investigators using paper case report forms designed specifically for this study. All data are entered into REDCap (see **Figure, Supplemental Digital Content 4**, http://links.lww.com/BOT/A861).

Data Analysis

The main statistical analyses will focus on RCT patients and will be conducted according to the intent-to-treat paradigm, which means all patients will be analyzed according to the treatment group to which they were randomized. The primary hypothesis evaluated using 2-sample *t*-based confidence intervals. Statistical procedures will be employed that use baseline covariates that are moderately or strongly predictive of outcomes (eg, severity of soft tissue damage, flap requirements, and defect size) to increase statistical precision (ie, power).[30] Regression modeling may be used, if concerns about confounding arise because of unexpected imbalances between treatment groups with respect to key prognostic baseline factors. Hierarchical modeling will be used, if concerns regarding the clustering of outcomes within centers emerge.

Also, a newly developed procedure that uses data from observational patients to construct a more precise estimator of the treatments in the RCT may be used.[30,31] As necessary, secondary analyses will also be conducted to address treatment crossovers.

Multiple imputation will be used to handle missing baseline covariates. Missing outcomes will not be imputed. Sensitivity analyses will be performed to evaluate the robustness of the trial results to various assumptions about the distribution of missing outcomes.[31]

DISCUSSION

This is the largest prospective randomized trial to evaluate the safety and efficacy of PO versus IV antibiotic use for postoperative wound infections. A number of challenges were encountered with implementation of the study including, low enrollment numbers, nonadherence, and identification of eligible patients whose insurance allowed flexibility in the administration of PO and IV antibiotics. Initially, the inclusion criteria were narrowly defined as long bone fractures that develop a deep wound infection with a positive intraoperative culture within 6 weeks of plate fixation. To address low enrollment numbers, inclusion criteria were expanded to include infections after internal fixation of injuries to the foot, clavicle, or pelvis and fusions of the subtalar, ankle, knee, wrist, or elbow joints. Time from fixation was also eliminated as an inclusion criterion because clinicians commonly manage infections that present later than 6 weeks postfixation and are faced with the same decision of mechanism of antibiotic delivery through PO or IV routes.[19] To further address low enrollment numbers, conference calls with sites that had not enrolled patients were conducted. These calls involved the study principal investigator, the Coordinating Center team, and the site principal investigator, coordinator, and infectious disease physician. The purpose of the calls was to identify issues preventing enrollment at individual sites and to assist with troubleshooting these issues. To address nonadherence, likely due to lack of equipoise of the infectious disease physicians at a few sites, the Coordinating Center created educational materials for the sites to more effectively engage the infectious disease team and familiarize them with study enrollment procedures. The enrollment rate doubled over a period of 6 months after distribution of these educational tools. Finally, we

experienced challenges in identifying financially eligible patients because of variation across among hospitals in the ability to provide antibiotics and different prescription coverage levels across insurance plans. To address this challenge, an observational cohort was added. In the observational study, the benefits of randomization are not preserved, that is, patients treated with PO may be different than patients treated with IV with respect to pretreatment risk factors related to the outcomes under investigation. In the combined analysis of the RCT and observational study, this issue will be addressed by adjusting the analysis using participant and injury characteristics that influence both decisions to enroll in the RCT and to opt for PO versus IV treatment within the observational study. Although this combined approach has the potential to provide extra precision, it may be biased if it is believed that there exist important unmeasured factors that are not included in the analysis. Nonetheless, this combined analysis will be supplemental to the RCT results, where randomization reduces the threats of selection bias.

A limitation of the study is lack of blinding of clinicians and patients. Other limitations include those typical of pragmatic trials in that the details of surgical treatment were left to the discretion of the site surgeons, which might lead to important variations in treatment that might harm the ability to detect a treatment effect. However, this design should also increase generalizability of the findings.

Major study strengths include the fact that the study is a prospective randomized trial, increasing the internal validity of the results. Additional strengths are the multicenter approach to patient recruitment and our broad inclusion criteria, both of which will make study results generalizable to everyday practice in trauma centers. The protocol was developed using a group of infectious disease specialists and experienced orthopaedic trauma surgeons. Overall, this study will provide important evidence to aid in decision making with regard to antibiotic delivery in this population.

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APPENDIX 1. CORPORATE AUTHORS

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