

Protocol

Annual Review III Date: February 2, 2017

Protocol Title: Efficacy of Oral Antibiotic Therapy compared to Intravenous Antibiotic Therapy for the Treatment of Diabetic Foot Osteomyelitis (CRO-OSTEOMYELITIS)

Protocol Version: 1.70 (Amendment 9)

Protocol Date: 11/18/2015

Principal Investigator: Michael Pinzur MD

Research Team: Michael Pinzur, Paul O' Keefe, Tammy Rhoda, Laurie Labuszewski PharmD, Katherine Dux, DPM, Tonya Crawford PharmD, Jorge Parada MD, Stephanie Kliethermes, PhD, William Adams, MA, Francis J. Rottier, DPM, Casey J. Holmes, Louise Lie, Nina Patel, DO, Infectious Diseases Fellow, Adam Schiff, MD

I. Abstract

The Infectious Diseases Society of America (IDSA) 2012 guidelines for the diagnosis and treatment of diabetic foot infections state that for the treatment of diabetic foot osteomyelitis “No data support the superiority of any specific antibiotic agent or treatment strategy, route, or duration of therapy.” [1] Traditionally, osteomyelitis has been treated with a long course of intravenous antibiotics, generally 6 weeks. Oral antibiotics with high bioavailability and adequate bone penetration have been shown in published studies to be effective for the treatment of osteomyelitis.[2]

We propose to conduct a prospective, single-center, randomized, open trial at Loyola University Medical Center (LUMC) comparing the efficacy of oral antibiotic therapy to intravenous (IV) antibiotic therapy for the treatment of diabetic foot osteomyelitis. We hypothesize that oral antibiotic therapy is equivalent to IV antibiotic therapy.

Bone/tissue cultures are obtained for all patients for clinical purposes and are sent to pathology for histologic examination and to the clinical microbiology laboratory for culture and susceptibility.

Patients will receive six weeks of IV or oral antibiotic therapy depending upon their randomization group. Primary outcomes at six months clinical follow-up will be no evidence of bone infection and resolution of ulcer.

II. Background and Significance/Preliminary Studies

Currently available literature is not adequate to determine the best agent, route, or duration of antibiotic therapy for the treatment of chronic osteomyelitis [1,2,3] The standard of therapy has been to treat patients with a

parenteral antibiotic for 4 to 6 weeks. In a recent literature review by Spellberg et al. it was concluded that oral and parenteral antibiotic therapy have similar cure rates for the treatment of chronic osteomyelitis.[2] Oral antibiotic therapy is associated with a lower risk to the patient due to avoiding the need of a central IV line. Additionally, oral therapy costs less than a course of IV antibiotics. Oral antibiotics with high bioavailability and good bone penetration include, fluoroquinolones, linezolid, trimethoprim/sulfamethoxazole (2 tabs bid), clindamycin and metronidazole. These antibiotics have been shown in recent studies to obtain levels in the bone that exceed MIC's of the targeted organisms. [2]

According to the IDSA 2012 guidelines for the treatment of diabetic foot infections, the diagnosis of osteomyelitis can be made via plain radiographs or MRI imaging (more sensitive). A bone scan can be considered if an MRI cannot be done. The preferred method of diagnosis is by bone culture and histology. The guidelines also recommend surgical debridement to healthy tissue for diabetic foot infections followed by antibiotic therapy. [1]

III. Study Aims

1. The Purpose of this study is to compare the efficacy of oral antibiotic therapy with IV antibiotic therapy for the treatment of diabetic foot osteomyelitis following surgical debridement.

Hypotheses: Oral Antibiotic Therapy is equivalent to IV Antibiotic Therapy for the Treatment of Diabetic Foot Osteomyelitis.

Outcomes will be assessed at six months:

- i. No evidence of bone infection. (absence of infection based on clinical examination and down-trending of inflammatory markers)
 - ii. Resolution of ulcer.
2. To biobank bone/tissue specimens obtained from all patients who participate in the study for future research purposes.

IV. Administrative Organization

This will be a prospective, single-center study at Loyola University Medical Center (LUMC). The Clinical Research Office (CRO) at Loyola will assist with the project.

V. Study Design

A prospective, randomized, single-center, open trial at Loyola University Medical Center will be conducted in adult diabetic patients with osteomyelitis involving the foot. Patients will be randomized into three groups:

1. Toe osteomyelitis (phalanges)
2. Midfoot osteomyelitis: infection distal to the tarsal-metatarsal joint up to the metatarsal-phalangeal joint.

3. Hindfoot osteomyelitis: infection distal to the ankle up to the tarsal-metatarsal joint.

Patients in each group will be randomized to receive either oral antibiotic therapy or IV antibiotic therapy for a minimum of 6 weeks.

Outcomes:

1. No evidence of bone infection at 6 months. (Clinical absence of infection)
2. Resolution of ulceration at 6 months.

VI. Study Procedures

A. Inclusion Criteria

18 years of age and older
Diagnosis of Diabetes Mellitus (Per past medical history documented in the patient medical record)
Foot osteomyelitis (distal to ankle)
Surgical debridement (in operating room)

B. Exclusion Criteria

Absolute neutrophil count (ANC) < 500
Pregnant or lactating patients
Patients with organisms resistant to oral therapy (In the IV and oral groups)
Internal hardware
Definitive amputations (BKA)
Limb ischemia (absent pedal pulses or ABI < 0.5)

Bone/tissue specimens are obtained for all patients for clinical purposes. These specimens are sent to pathology for histologic examination and to the clinical microbiology laboratory for culture and susceptibility. Ulcers and wounds will be measured at all clinical appointments.

Any remaining specimens beyond what is needed for clinical purposes (if any) will be stored as defined in the IRB approved Clinical Research Office Biospecimen Repository (LU# 204853).

Until cultures results are available, patients will receive IV antibiotics (i.e., usually for the first 3 to 5 days). Once the culture results are known, the patient will be assigned an antibiotic regimen (IV or oral) depending on the randomization group and based upon the organisms isolated and their susceptibilities. Antibiotic therapy will be administered for a minimum of six weeks.

Patients will be followed by the Infectious Diseases service and either the Orthopedics or Podiatry service in the hospital. After discharge, the patients are seen clinically every 2 weeks by either the Orthopedics, Podiatry, or Infectious

Diseases service. At specific follow-up appointments, we will collect laboratory relevant laboratory data:

Table 1. Laboratory test monitoring schedule.

Laboratory Test	Oral antibiotic group	IV antibiotic group
CBC w/ dif	Baseline & weeks 3 & 6	Baseline & weekly
BUN	Baseline & weeks 3 & 6	Baseline & weekly
Creatinine	Baseline & weeks 3 & 6	Baseline & weekly
ESR	Baseline & weeks 3 & 6	Baseline & weeks 3 & 6
CRP	Baseline & weeks 3 & 6	Baseline & weeks 3 & 6
CK	N/A	Baseline & weekly
Vancomycin concentration	N/A	Weekly
Albumin	Baseline	Baseline
HgA1c	Baseline	Baseline

N/A-not applicable

EMPIRIC IV THERAPY:

Initial IV therapies for patients before the availability of their culture and susceptibility data include:

1. piperacillin/tazobactam (Zosyn) **OR**

PCN ALLERGY with rash: cefepime + metronidazole* **OR**

SEVERE PCN ALLERGY: aztreonam + vancomycin + metronidazole*

2. If patient has a history of MRSA (methicillin resistant staphylococcus aureus) infection or colonization then add vancomycin **OR**

VANCOMYCIN ALLERGY/INTOLERANCE : daptomycin or linezolid*

3. If history of ESBL (extended spectrum beta-lactamase producing organism):
Use meropenem instead of piperacillin/tazobactam or cefepime + metronidazole (meropenem cannot be used in patients with severe PCN allergies without desensitization).

(*linezolid and metronidazole will be given orally in all patients (empiric, IV and oral groups) unless oral administration is not feasible)).

When culture and susceptibility data are available, therapy will be altered to as narrow spectrum coverage as possible in both study groups.

ORAL THERAPY OPTIONS:

Once culture and susceptibility data are available, patients randomized to the oral therapy group will be converted from IV therapy to one or more of the oral antibiotic choices included in table 2.

Table 2. Oral antibiotic options

Oral Antibiotic	Dose	Organisms covered
SMX-TMP	2 double strength tablets (DS) every 12 hours* [2]	MSSA, MRSA, susceptible gram negative bacilli
clindamycin	600mg every 8 hours [4]	MSSA, MRSA, Streptococcus, anaerobes
linezolid	600mg every 12 hours	MSSA, MRSA, Streptococcus, VRE
moxifloxacin	400mg every 24 hours	Streptococcus, gram negative bacilli except pseudomonas
ciprofloxacin	750mg every 12 hours* [2]	pseudomonas and other gram negative bacilli
metronidazole	500mg every 8 hours	anaerobes

MSSA- methicillin sensitive staphylococcus aureus, MRSA- methicillin resistant staphylococcus aureus, VRE- vancomycin resistant enterococcus.

*dose adjustment required for renal dysfunction

C. Recruitment procedures

Participants will be approached in the hospital or in the outpatient clinics by a qualified member of the research team and informed consent will be obtained in a private consult room prior to surgery by the PI or a research team member

D. Screening procedures

All ordered tests and procedures in the study protocol are part of standard care.

Patients who do not meet inclusion criteria for the study or who do not agree to participate in the study will continue to be treated with appropriate, routine clinical care.

E. Randomization procedures

This is an open study. The randomization table will be generated by Stephanie Kliethermes, PhD, who is the principle biostatistician for this trial using SAS version 9.2)

F. Study Intervention

This is an open study. The antibiotics used in this study are routinely used in clinical practice. The oral antibiotics to be used in the study were chosen because they have a high oral bioavailability and have been shown in the medical literature to have adequate bone concentrations when given orally to treat osteomyelitis.

Patients receiving IV antibiotics will continue to receive such clinical therapy as described by their healthcare provider, via a central line under the care of a home care agency, nursing home, rehabilitation center or infusion center consistent with current clinical practice. Laboratory studies will be monitored with dosage modifications as necessary (see Table 1).

G. Study Assessments and Activities

Bone/tissue specimens are obtained for all patients for clinical purposes. These specimens will be sent to pathology for histologic examination and to the clinical microbiology laboratory for culture and susceptibility. Any extraneous bone/tissue that would routinely be discarded will be collected and stored for Dr. Katherine Radek's study (LU#202919) and used for research activities stated in the approved protocol. The CRO will act as the honest broker and following signing of a usage agreement to release the biological specimens, the de-identified bone/tissue samples will be retrieved and relevant phenotype information will be provided in a de-identified manner. Data will be collected prospectively, pooled, statistically analyzed and formatted for presentation at regional or national meetings and/or publication in peer reviewed surgical/medical journals for research purposes only.

Debridement will be accomplished with either sharp debridement and/or pulsed ultrasound. Surgery will be considered adequate when all purulent or dysvascular tissue has been removed and margins are clinically viable (i.e. excision of all infected tissues). If the final surgery is performed at the level of infection, the wound (s) will be initially managed with open treatment. Secondary wound closure vs. healing by secondary intention will be decided by the operating surgeon. If the surgery is performed proximal to the level of infection, i.e. amputation, the wound will be primary closed. [1,5]

Diabetic foot wounds will be classified according to the Wagner system. Ulcers and wounds will be measured to determine size and depth at baseline and at follow up visits. Baseline measurements will be obtained post-debridement and measurements will be obtained at each follow-up visit until closure of the wound is obtained.

Laboratory tests will be completed at baseline and then weekly for patients on IV antibiotics and oral linezolid (CBCw/ dif, BUN & creatinine). Patients on oral antibiotics (other than linezolid) will get the same laboratory tests at baseline and at weeks 3 and 6. A baseline ESR and CRP will be obtained on all patients and repeated at weeks 3 and 6. Albumin and Hg A1c will be collected for all patients at baseline. Patients receiving daptomycin will have creatinine kinase (CK) tested once weekly in addition to other labs as above. Vancomycin concentrations will be obtained at least once weekly. All laboratory screenings are considered routine clinical care.

Patients will be followed by the Infectious Diseases service and either the Orthopedics or Podiatry service in the hospital. After discharge the patients will be seen every 2 weeks by either the Orthopedics, Podiatry, or Infectious Diseases service. This is considered routine clinical care.

Additional variables that will be collected in this study include the results of the following tests: X-ray, CT scan, MRI, bone scan, and white blood cell scan, pathology reports, surgical reports and culture results. These assessments will have been ordered by the patient's healthcare provider and are considered routine clinical care.

VII. Safety Monitoring Plan

Because the therapy agents, regardless of their route of administration, are considered routine clinical care, adverse reactions will be managed on an individual basis by the patient's healthcare providers.

If an antibiotic needs to be changed due to intolerance or toxicity in a patient randomized to the oral antibiotic group, the patient will remain in the study if another oral antibiotic is substituted by his/her healthcare provider. If a patient in the oral antibiotic group requires a change to an IV antibiotic, then the patient will be considered to have failed oral therapy

VIII. Power Analysis / Analysis Plan

Formula based Sample Size Calculations (no adjustment for infection group)

As the assumed proportion of individuals experiencing bone infection after 6 months increases, the sample size decreases. This is because the probability is shifting further away from 50%. Assuming a non-inferiority margin of 10% results in lower sample size needs than assuming a non-inferiority margin of 5%.

Proportion without Bone Infection	60%		70%		80%		90%	
Non-inferiority margin	5%	10%	5%	10%	5%	10%	5%	10%
$\alpha=0.05$	2376	594	2078	520	1584	396	892	224
$\alpha=0.01$	3878	964	3374	844	2570	644	1446	362

Simulation based Sample Size Calculations (adjusting for infection group)

These calculations assume an equal number of patients are enrolled in each of the three groups (toe, midfoot, hindfoot) and that there is no difference in the proportion of individuals who experience bone infection in any group. The sample sizes are slightly larger than those in the first table because we are now accounting for the stratification by group.

Proportion without Bone Infection	60%		70%		80%		90%	
Non-inferiority margin	5%	10%	5%	10%	5%	10%	5%	10%
$\alpha=0.05$	2394	604	2102	533	1606	400	898	231
$\alpha=0.01$	3896	990	3418	857	2619	659	1454	378

Based on the power analysis above, the goal sample size will be 224 patients with $\alpha=0.05$, a non-inferiority margin of 10% and a 90% cure rate (90% without bone infection after 6 months). We will request to consent up to 300 people to account for individuals who are excluded due to abnormal laboratory values and would not be able to continue with their participation.

IX. Literature Cited

1. Lipsky B, Berendt A, Cornia P, et al. 2012 Infectious Diseases Society of America Clinical Practice Guideline for the Diagnosis and Treatment of Diabetic Foot Infections. CID 2012;54(12):1679-84.
2. Spellberg B and Lipsky B. Systemic Antibiotic Therapy for Chronic Osteomyelitis in Adults. CID 2012;54(#):393-407
3. Lazzarini L, Lipsky B, Mader J. Antibiotic Treatment of Osteomyelitis: What Have we Learned from 30 years of Clinical Trials. Int J Infect Dis 2005;9:127-138

4. Bouazza N, Pestre V, Jullien V, et al. Population pharmacokinetics of Clindamycin Orally and Intravenously Administered in Patients with Osteomyelitis. *Br J Clin Pharmacol* 2012;74(6):971-77.
5. Wukich DK, Armstrong DG, Attinger CE, Boulton AJ, Burns PR, Frykberg RG, Hellman R, Kim PJ, Lipsky BA, Pile JC, Pinzur MS, Siminerio L. Inpatient management of diabetic foot disorders: a clinical guide. *Diabetes Care*. 2013 Sep;36(9):2862-71.
6. Pinzur M, Fil J, Belmares J. et al. Treatment of Osteomyelitis in Charcot Foot with Single-Stage Resection of Infection, Correction of Deformity, and Maintenance with Ring Fixation. *Foot Ankle Int.*2012;33(12)1069-74.

X. Summary of Amendments

1. Protocol 1.00 → 1.10: (dated 3/21/14 – WAdams) (Amendment 1)

1. Added research team members Anilrudh Venugopal, Michael Pinzur, Paul O' Keefe, and Tammy Rhoda

2. Protocol 1.10 → 1.20: (dated 7/14/14 – WAdams) (Amendment 2)

1. Removed research team member Anilrudh Venugopal
2. Removed exclusion criterion: "Bone biopsy histology negative for inflammation"
3. Removed exclusion criterion: "Negative bone/tissue cultures and no evidence of infection demonstrated on microscopic examination"
4. Minor changes to the ICD that do not affect meaning or interpretation.

3. Protocol 1.20 → 1.30: (dated 7/14/14 – WAdams) (Amendment 3)

1. Removed inclusion criterion: Bone biopsy with histologic evidence of acute or chronic inflammation

4. Protocol 1.30 → 1.40: (dated 8/19/14 – DMartin) (Amendment 4)

1. Added research activities which include sharing patient specimens Under Study Assessments

5. Protocol 1.40: did not change version (dated 10/06/14 – TRhoda) (Amendment 5)

1. Added Research Team Member: Francis J. Rottier, DPM
- 6. Protocol 1.30 → 1.40: (Should have been 1.40 → 1.50) (dated 10/27/14 – DMartin) (Amendment 6)**
 1. Added an additional specific aim and study procedure to include banking left over materials for future research purposes in the CRO-BIOREPOSITORY
 2. Added Research Team Members: Casey J. Holmes, Louise Lie
- 7. Protocol 1.40 → 1.50: (dated 7/2/2015 – TRhoda) (Amendment 7)**
 1. Added Research Team Members: Adam Schiff, MD and Nina Patel, DO, Infectious Diseases Fellow
- 8. Protocol 1.50 → 1.60: (dated 7/13/2015 – TRhoda) (Amendment 8)**
 1. Amendment 7 – No Action Due to Adam Schiff due for Citi Training Refresher Modules. Remove him from Protocol and add Research Team Member: Nina Patel, DO, Infectious Diseases Fellow
- 9. Protocol 1.60 → 1.70: (dated 11/18/2015 – TRhoda) (Amendment 9)**
 1. Amendment 9– Add Research Team Member Adam Schiff - Completed Citi Training Refresher Modules.