

AWARD NUMBER: W81XWH-19-2-0062

TITLE: Evaluation of a New Strategy for Protocolized Antibiotic Care for Severe Open Fractures

PRINCIPAL INVESTIGATOR: Michael Bosse, MD

**CONTRACTING ORGANIZATION: Charlotte-Mecklenburg Hospital Authority
d/b/a Atrium Health, Charlotte, NC**

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14. ABSTRACT Background. Infection remains the most common and significant complication following high-energy open fractures, with rates ranging from 15-40% ¹⁻⁸ . Up to 15% of recent combat casualties develop osteomyelitis. ^{2,4,9,10} At present, antibiotics are delivered in an empiric fashion, as the surgeon does not know the bacterial profile of the open fracture wound at the time of injury or at the time of wound coverage/closure. Building on conclusions from a prospective observational study that evaluated the bioburden of severe lower extremity wounds sampled at the time of final wound coverage or closure, this project will study the impact of a new antibiotic delivery <i>treatment strategy</i> compared to the existing standard of care antibiotic <i>prophylaxis strategy</i> to evaluate the impact on deep SSI. Objective. The overall objective of the proposed study is to perform a PRCT in order to compare the antibiotic and infection related outcomes of a new antibiotic strategy for use in the care of severe open extremity fractures to the current standard of care. Study Design. This study will be conducted in 30 established METRC level 1 trauma centers. The patients will be randomized as close to admission as possible to either 1) Standard of Care (SOC) prophylactic open fracture protocol or 2) experimental protocol (SEXTANT) that will direct a wound bioburden targeted systemic and topical vancomycin powder and tobramycin powder antibiotic treatment at the time of final wound closure/coverage. The study will compare results of the current SOC prophylactic coverage to the SEXTANT protocol					
15. SUBJECT TERMS Orthopaedic trauma; surgical site infection; local antibiotics					
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1. INTRODUCTION:

Background. Infection remains the most common and significant complication following high-energy open fractures, with rates ranging from 15-40%¹⁻⁸. Up to 15% of recent combat casualties develop osteomyelitis.^{2,4,9,10} At present, antibiotics are delivered in an empiric fashion, as the surgeon does not know the bacterial profile of the open fracture wound at the time of injury or at the time of wound coverage/closure. Building on conclusions from a prospective observational study that evaluated the bioburden of severe lower extremity wounds sampled at the time of final wound coverage or closure, this project will study the impact of a new antibiotic delivery *treatment strategy* compared to the existing standard of care antibiotic *prophylaxis strategy* to evaluate the impact on deep SSI.

Objective. The overall objective of the proposed study is to perform a PRCT in order to compare the antibiotic and infection related outcomes of a new antibiotic strategy for use in the care of severe open extremity fractures to the current standard of care.

2. KEYWORDS:

Orthopaedic trauma; surgical site infection; local antibiotics

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Study Specific Aims

- Specific Aim 1: To compare the infection rates of the current severe open fracture prophylactic antibiotic strategy to a revised SEXTANT treatment strategy designed to address the modern wound bioburden at the time of wound closure.
- Specific Aim 2: To compare the terminal bioburden of the wounds at the time of definitive closure / coverage as sampled by standard tissue microbiology.
- Specific Aim 3: To compare rates of antibiotic-related serious adverse events (SAEs) of the two treatment groups.
- Exploratory Aim 4: To pilot the use of available and emerging rapid PCR platforms for wound pathogen identification in a sub-cohort of patients.

Major Task 1: Study Initiation

Subtask 1: Finalize protocol

Subtask 2: Develop case report forms for data capture – in progress

Subtask 3: Program and pilot test REDCap – in progress

Subtask 4: Obtain initial IRB approval – pending

Subtask 5: Distribute approved protocol and obtain IRB approval via single IRB

What was accomplished under these goals?

Major Activities: During this quarter, we finalized the protocol and prepared for IRB submission. We have also worked on the case report forms and quality assurance programming.

Specific Objectives: (1) Revised budget has been approved; (2) convened protocol committee meetings to finalize the protocol; (3) the protocol and CRFs have been finalized.

Significant Results or Key Outcomes: None to report

Other Achievements: None to report.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

We plan to pause initiation activities from 10/1/2020-12/31/2020 due to COVID-19. During this period, Carolinas Medical Center/Atrium Health (the lead site) will submit materials to the single IRB and receive approval. Our goal will be to reopen on 1/1/2021 with a target of 3/1/2021 for the initiation of enrollment.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS:

We plan to pause initiation activities from 10/1/2020-12/31/2020 due to COVID-19. During this period, Carolinas Medical Center/Atrium Health (the lead site) will submit materials to the single IRB and receive approval. Our goal will be to reopen on 1/1/2021 with a target of 3/1/2021 for the initiation of enrollment. Therefore, we are requesting a shift in the planned budget and timeline to account for the pause of one quarter.

Changes in approach and reasons for change

Actual or anticipated problems or delays and actions or plans to resolve them

It is possible that the ongoing pandemic will lead to further delays. We are working with the sites to anticipate any issues related to implementation.

Changes that had a significant impact on expenditures

See above.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**
Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

Nothing to report.

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

Other Products

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Personnel	Role	Effort
Rachel Seymour	Co-I	1.25%

METRC Coordinating Center (Yr1 - Annual)

Personnel	Role	Effort
Renan Castillo	PI, MCC Director	10%
Richard Thompson	Biostatistician	10%
Anthony Carlini	Project Director	5%
Suna Chung	Project Director	9%
Susan Collins	Study Manager	15%
Elias Weston-Farber	Programmer	5%
Jack Dagg	Data Analyst	6%
Manisha Kumar	Finance Manager	5%

Role split w/ Anthony Carlini

Replaced Andre Hackman

Replaced Yanjie Huang

Financials (As of Yr1 - Annual)

Award Amount

Projected expenditure to date
Actual expenditure to date

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Dr. Michael Bosse has retired from clinical duty at our institution but continues to hold an academic appointment in which he can participate in research. He will remain the PI on this project to provide scientific design and oversight and clinical oversight for Carolinas Medical Center will be assumed (upon approval) by Madhav Karunakar. Dr. Karunakar's biosketch is enclosed for review.

Dr. Bosse will remain 10% on the project as he is the national PI and will lead training for surgeons and ID physician Co-I as well for research coordinators. Dr. Bosse will also supervise data quality and assurance and serve as chair of the adjudication committee.

We are requesting to add 5% for Dr. Karunakar's time to perform the clinical duties.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:



Evaluation of a New Strategy for Protocolized Antibiotic Care for Severe Open Fractures

PI: Michael Bosse, MD

Org: Carolinas Medical Center

Award Amount: \$3,000,000

Study Aims

Hypothesis: Patients treated with Severe Extremity Trauma Topical and Systemic Antibiotic Protocol (SEXTANT) will have fewer surgical site infections than those treated with standard of care (SOC).

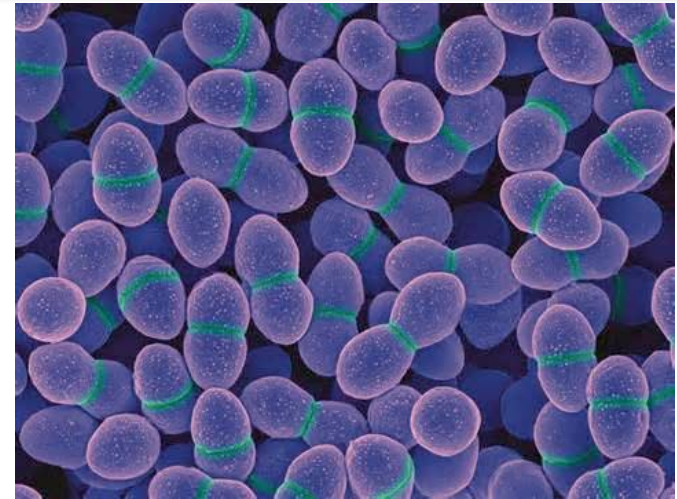
Specific Aim 1: To compare the infection rates of the current severe open fracture prophylactic antibiotic strategy to a revised SEXTANT treatment strategy designed to address the modern wound bioburden at the time of wound closure.

Specific Aim 2: To compare the terminal bioburden of the wounds at the time of definitive closure / coverage as sampled by standard tissue microbiology.

Specific Aim 3: To compare rates of antibiotic-related serious adverse events (SAEs) of the two treatment groups.

Exploratory Aim 4: To pilot the use of available and emerging rapid PCR platforms for wound pathogen identification in a sub-cohort of patients.

Approach: Conduct a prospective, randomized clinical trial of 800 patients with Gustilo type IIIB and selected IIIA fractures of the upper and lower extremity, excluding the hand and forefoot. Patients will be assigned to either SOC or SETTSAP. Primary outcome is deep infection. Secondary outcomes include presence of resistant organisms and antibiotic-related serious adverse events.



Enterococcus, a predominant species in positive cultures

Timeline and Cost

Activities	CY	19	20	21	22
Protocol Development and Approval		█			
Patient Enrollment and baseline data collection			█		
Follow-up and data quality assurance activities			█	█	
Data analysis and Reporting					█
Estimated Budget (\$3000K)		\$750	\$1000	\$750	\$500

Goals/Milestones

CY19 Goals – Protocol Development and Approval

X Convene protocol committee and develop study protocol and all associated case report forms

CY20 Goal – IRB approval

Submit protocol for master approval at PI site and Johns Hopkins

Submit protocol for approval at all participating centers

CY19-21 Goal – Enrollment and Data Collection

Enroll patients and obtain follow-up visits

Collect study data

Engage in monitoring and quality assurance activities to ensure high quality data

CY22 Goal – Reporting

Complete data analysis and reporting requirements

Comments/Challenges/Issues/Concerns: n/a

Budget Expenditure to Date

Projected Expenditure: Proposed: \$ \$838,483

Actual Expenditure: \$72,199.08

Updated: 11/1/2020