CORTICES
ADVANCING EVIDENCE-BASED ORTHOPEDIC CARE

Retrospective Study Protocol

TITLE: The Management and Outcomes of Pediatric Type III Open Fractures

Study Summary: This multicenter retrospective cohort study will evaluate infection and complication outcomes in pediatric patients (0–18 years) treated for Gustilo-Anderson Type III open long bone fractures at CORTICES institutions between 2015 and 2026. The primary objective is to determine the 180-day post-injury infection rate and characterize infection severity, antibiotic requirements, and need for surgical washout. Secondary aims will assess the relationship between antibiotic management, perioperative factors, and the development of infection, as well as estimate the overall 180-day complication rate. Demographic, injury, timing, antibiotic, surgical, and follow-up data will be collected through standardized chart review and entered into a multicenter REDCap database. By leveraging a large, multicenter pediatric cohort, this study seeks to characterize current treatment practices and identify factors associated with adverse outcomes in children with severe open fractures.

A. Specific Aims/Objectives

Primary Aim: To estimate the 180-day post emergency department (ED) admission infection rate in pediatric patients aged 0-18 years undergoing treatment for long bone Type III open fractures, excluding pelvic fractures and lawnmower and firearm mechanisms of injury, at CORTICES institutions between January 2015 to May 2026.

Primary Hypothesis: We hypothesize that in pediatric patients aged 0-18 years who underwent treatment for Type III open fractures at CORTICES sites between January 2015 to May 2026, the 180-day post emergency department (ED) admission infection rate is between 2.8-40.5%.

Primary Outcome:

- Infection (binary, y/n)
  - Infection type (deep/superficial; categorical)
  - Infection requiring antibiotics (IV/PO; categorical)
  - Infection requiring surgical washout (binary, y/n)

Secondary Aims, Hypotheses, Outcomes:

Aim 1: To assess the association between time to antibiotics administration, type of antibiotics administered, and duration of IV antibiotics with the occurrence of 180-day post ED admission infection in pediatric long bone Type III open fracture patients aged 0-18 years treated at CORTICES institutions, excluding pelvic fractures and lawnmower and firearm mechanisms of injury,

Hypothesis: We hypothesize that in patients aged ≤18 seen at CORTICES institutions for Type III open fractures, a shorter time to antibiotic administration, the use of a combination of antibiotics, and a longer duration of IV antibiotics is associated with lower rates of 180-day post ED admission infection following treatment.

Outcome: Infection (binary, y/n)

Aim 2: To assess the association between perioperative factors and the occurrence of 180-day post ED admission infection in pediatric Type III long bone open fracture patients aged 0-18 treated at CORTICES sites between January 2015- May 2026, excluding pelvic fractures and lawnmower and firearm mechanisms of injury.

Hypothesis: We hypothesize that in patients aged ≤18 seen at CORTICES sites for Type III open fractures, a longer time to the OR and undergoing more than one surgical procedure results in a higher occurrence of 180-day post ED admission infections following treatment.

Outcome: Infection (binary, y/n)

Aim 3: To estimate the 180-day post ED admission complication rate in pediatric patients aged 0-18 undergoing treatment for Type III open fractures at CORTICES institutions between January 2015 - May 2026, excluding pelvic fractures and lawnmower and firearm mechanisms of injury.

Hypothesis: We hypothesize that in pediatric patients who underwent treatment for Type III open fractures at CORTICES institutions between January 2015 - May 2026, the 180-day post ED admission complication rate is around 5%.

Outcome: 180-day complications (binary, y/n)

B. Background and significance

(Justify the study's clinical importance with minimum of 5 relevant references. Noting limited knowledge to date or controversy alone is insufficient.)

It is the standard of care to administer IV antibiotics upon arrival to the emergency department for an open fracture to prevent infection, as time to antibiotic administration is a critical factor in the prevention of infection.[1,2] Despite this urgency, there is no single gold standard for the selection and timing of antibiotic administration based on Gustilo-Anderson (GA) fracture type. In fact, institutions and providers differ greatly in which antibiotics they chose and how quickly they are administered.[3-6] While GA Type I and II open fractures have lower rates of infection and typically need protection against gram positive organisms, Type III open fractures have a higher rate of infection and benefit from broad spectrum coverage.[7,8] There is currently minimal guidance about the best practices for antibiotic administration for pediatric Type III fractures, where most protocols are extrapolated from adult data without validation in pediatric populations.

A recent CORTICES multicenter survey revealed consistent antibiotic regimen recommendations for pediatric Type I-II open fractures across surveyed Level-1 trauma centers, but identified substantial practice variation for the optimal pediatric antibiotic protocol for the more severe Type III open fractures. To learn more about this research gap, we retrospectively reviewed 33 patients with long bone Type III open fractures treated at Boston Children's Hospital between 2014-24. Cohort demographics, clinical and injury characteristics, hospital management, functional outcomes, and infection and complication rates were analyzed. Even within a single-institution, antibiotic regimens for treatment of these injuries were not consistent and highlights a lack of standardized antibiotic protocols. We also found a substantial infection and complication burden, affecting 23% and 59% of our pediatric cohort respectively. Infections were more common in patients with tibia fractures and those who had been a pedestrian or biker struck by a motor vehicle. Further multicenter research is warranted to determine the optimal antibiotic regimen to reduce the risk of postoperative infections and complications in this patient population.

Building off our previous work, this proposed multicenter retrospective study aims to identify antibiotic practice patterns and their influence on functional outcomes and the development of postoperative infections and complications in pediatric long bone Type III open fractures treated at Level-1 pediatric trauma centers.

----------*Cited references listed at bottom of protocol*----------

C. Preliminary Studies *(Prior work by the investigators, even if unpublished)*

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to determine the optimal antibiotic regimen to reduce the risk of postoperative infections and complications in this patient population.

D. Design and Methods

(1) Study Design

Retrospective
☒ Cohort ☐ Case-cohort ☐ Case-control ☐ Case series ☐ Other_____
Multicenter? ☒ Yes ☐ No
☒ All sites ☐ Selected sites

(2) Patient Selection and Inclusion/Exclusion Criteria

Inclusion criteria:

- Between 0 to ≤18 years of age
- Diagnosis of GA Type III Open Fracture of a long bone
- Treated between 01/01/2015 to 05/31/2026

Exclusion criteria:

- Immunocompromised patients
- Fractures of the skull, face, hand, foot, or pelvis
- Revision procedures
- Lawnmower or firearm mechanism of injury

(2) Description of Study Treatments or Exposures/Predictors

Since this study is an observational retrospective cohort study, no study treatments will be used. As our goal is to assess the rate of infection and complications associated with pediatric Type III open long bone fractures, our exposures and predictors will focus on patient demographics, injury characteristics, clinical timing data, antibiotic and surgical data, as well as postoperative data. 180 days will be used as a minimum follow-up window for the infection and complication rate calculations; however, follow-up data beyond this minimum will be captured if available.

Patient & Demographic Data

- Age at injury (discrete; years)
- Sex at birth (binary; male/female)
- Ethnicity (binary; Hispanic/Latino/a/x/ or no)
- Race (categorical)
    - White
    - Black or African American
    - Native American/Alaskan Native
    - Asian
    - Native Hawaiian/Pacific Islander
    - Other
    - Unknown
- Height (continuous; cm)
- Weight (continuous; kg)
- BMI (ratio)
- Serious comorbidities (binary; y/n)
    - Comorbidity description (free text)

Injury Characteristics

- Date of injury
- Mechanism of injury (categorical)
    - Motor vehicle collision
        - Driver or passenger

    - Pedestrian struck by motor vehicle
    - Bicycle or scooter
        - Motor vehicle involved (binary; yes/no)
    - E-bike or E-scooter
        - Motor vehicle involved (binary; yes/no)
    - Playground
    - Trampoline
    - Sport
    - Fall
    - ATV/UTV
    - Other
- Multiple Type III open fractures (binary; yes/no)
    - Number of Type III open fractures (count; 2,3,4+)
- Other fractures sustained (binary; y/n)
    - Fracture description
- Injury Severity Score (ISS) (categorical in terms of severity)
    - Mild (1–8)
    - Moderate (9–15)
    - Severe (16–75)
- Polytrauma (binary; y/n)
- Non-orthopaedic injuries (binary; y/n)
    - Non-orthopaedic surgery required (binary; y/n)
    - Type of non-orthopaedic surgery (if yes, categorical)
        - General/Trauma Surgery
        - Plastic Surgery
        - Urology
        - Neurosurgery
        - Vascular Surgery
        - Oral & Maxillofacial Surgery
        - Dental
        - Other
- Head injury (binary; y/n)

Fracture Characteristics
(Collected for Type III open fracture at each limb/extremity using repeating instruments)
- Open fracture location
    - Femur
    - Tibia/Fibula
    - Humerus
    - Radius/Ulna
- Gustilo-Anderson subtype
    - IIIA
    - IIIB
    - IIIC
- AO/OTA fracture classification (To be completed by surgeon)
- Gross contamination present
- Open wound size
    - <1 cm
    - 1–10 cm
    - 10 cm
    - Unknown

Surgical Characteristics
(Collected for Type III open fracture occurring at each limb/extremity)
Overall Surgical Data
- Number of orthopaedic surgeries during index hospitalization (discrete)

For Each Surgical Procedure Performed

- Procedure date (date)
- Bone stabilization method (categorical checkbox)
    - Internal fixation
    - External fixation
    - Percutaneous pin fixation
    - Cast/splint only
    - None
    - Other
- Procedure specialty (categorical checkbox)
    - Orthopaedics
    - Plastic Surgery
    - Other
- Soft tissue procedures (categorical checkbox)
    - Irrigation & debridement
    - Complete primary closure
    - Partial primary closure
    - Delayed primary closure
    - Local/rotational flap
    - Free flap
    - Skin graft
    - Wound VAC
    - Secondary intention wound care
    - Antibiotic bead/powder
    - Fasciotomy
    - Amputation
    - Other

Wound Closure Characteristics

- Definitive wound closure achieved (binary; y/n)
- Number of procedures required to achieve closure (discrete)
- Date of definitive wound closure
- Time to wound closure (number of days)
- Date of final wound management procedure (if not closed)
- Time to final wound management (number of days)

Fixation Characteristics

- Date of definitive fracture fixation
- Time to definitive fixation (number of days)

Hospital Course & Timing Data

- ED admission date/time
- ED arrival mode (categorical)
    - Ambulance
    - Medical flight
    - Walk/private transport
    - Transfer from outside hospital
- Admitting service (categorical)
    - Orthopaedics
    - Trauma
    - General Surgery
    - Plastic Surgery
    - ICU
    - Other
- Index surgery start date/time
- Index surgery end date/time

- Operative time (minutes)
- Time from ED admission to OR (hours)
- Hospital discharge date/time
- Length of stay (days)

Antibiotic Data

- Date/time of first IV antibiotic administration
- Time from ED admission to IV antibiotics (minutes)
- Initial IV antibiotic(s) (categorical checkbox)
    - Ampicillin
    - Unasyn
    - Cefazolin
    - Cefepime
    - Ceftriaxone
    - Ciprofloxacin
    - Clindamycin
    - Gentamicin
    - Linezolid
    - Meropenem
    - Metronidazole
    - Penicillin
    - Piperacillin/Tazobactam (Zosyn)
    - Tobramycin
    - Vancomycin
    - Fluconazole
    - Voriconazole
    - Other
- Additional IV antibiotics administered within first 24 hours (categorical checkbox; *same list of antibiotics as above*)
- Date/time of final IV antibiotic administration
- Duration of IV antibiotic therapy (number of days)
- Oral antibiotics prescribed (binary; y/n)
    - Oral antibiotic type (categorical checkbox)
        - Augmentin
        - Bactrim
        - Cephalexin
        - Ciprofloxacin
        - Clindamycin
        - Doxycycline
        - Levofloxacin
        - Rifampin
        - Other
    - Start date
    - Stop date
    - Duration of oral antibiotic therapy (number of days)

Clinical Follow-up & Outcomes

- Date of last orthopaedic follow-up
- Total follow-up duration (days) (ED admission to date of last recorded follow-up; months)
- Full return to activity/clinical recovery (binary; y/n)

Fracture Healing

- Radiographic union date (for fracture at each limb/extremity) (To be completed by surgeon)
- Time to radiographic union (number of days)

Postoperative Complications

- Any complication (binary; yes/no)

- Complication type (if yes, categorical checkbox)
    - Unexpected return to ED
    - Unexpected return to OR/additional surgery
    - Infection
    - Wound/surgical site complication
    - Delayed union/nonunion (>180 days)
    - Acute compartment syndrome
    - Amputation/loss of limb
    - Neurologic deficit
    - Vascular injury
    - DVT/PE
    - Sepsis
    - Death
    - Other
- First recorded complication date
- Complication description (text)

Additional Surgical Procedures After Discharge (categorical checkbox)

- Irrigation & debridement
- Hardware removal
- Revision fixation
- Soft tissue coverage
- Fasciotomy
- Antibiotic bead placement
- Other

Infection Characteristics

- Postoperative infection type (categorical)
    - Superficial
    - Deep
- Infection requiring (if infection, binary; y/n):
    - IV antibiotics
    - Oral antibiotics
    - Surgical washout
- Clavien-Dindo-Sink (CDS) Complication Grade (categorical; Grade I, II, III, IV, V)

(4) Definition of Primary and Secondary Outcomes/Endpoints

What is <u>Primary Outcome</u>? Infection (binary; y/n)

At what single time point will it be assessed to evaluate the primary aim?

At a minimum of 180-days postoperatively

How is it measured and what "score" is considered significant?

Binary: A 'yes' is significant, a 'no' is not

<u>Secondary Outcome(s)</u> and when it/they will be assessed?

Complications (binary; y/n)

A minimum of 180-days postoperatively

Binary: A 'yes' is significant, a 'no' is not

(5) Data Collection Methods, *(How to find patients, what CPT/ICD codes to use, search strategy, will it be chart review, radiographic measurements)*

Eligible patients will be identified via text searches and/or chart review using ICD9/10 codes. The keywords for the text search include "GA Type III", "Grade III", and "open fracture". These search terms are often present in orthopaedic consultation notes, orthopaedic clinic visit notes, operative reports, and ED admission notes.

For ICD-10 searches, the letter 'C' in the final position indicates a type III open fracture. The base codes for each eligible bone are as follows:

Femur -- S72.XXXC
Tibia/Fibula -- S82.XXXC
Humerus -- S42.XXXC
Radius/Ulna -- S52.XXXC

For ICD-9 codes, eligible patients will fall within the code range 810-829 with an odd value after the decimal point (ex: 810.3).

CPT codes 11010, 11011, and 11012 should be excluded as these refer to general irrigation & debridement procedures and are not fracture specific.

The resulting data query should be screened to remove ineligible patients prior to collecting data. Patients with pelvic fractures and fractures caused by lawnmower and ballistic injury mechanisms will be marked in the REDCap screening form but excluded from the main analysis. Chart review on eligible patients can then be performed.

An external REDCap database will be created for data entry, where each site will enter de-identified data.

(6) Proposed Study Timeline *(11/2025 – 09/2027)*

- Protocol Design and Variable list: 1 months
- IRB and DUA: 1 month
- Database Building and Alpha testing: 3 months
- Beta-testing: 3 months
- Data Collection (across all sites): 3-4 months
- Data Cleaning: 2 months
- Abstract Submission: 1-2 months
- Manuscript Writing: 3 months
- Submission for Publication: 3 months

E. Data Management Methods

Where will data be entered and stored? *Check all that apply.*

☒ REDCap ☒ Excel ☐ Other, specify:

If multiple checked, please specify why: Excel will be used to confirm patient eligibility for this study prior to entering de-identified data into an external REDCap. A link between the REDCap Study ID and the patient MRN will need to be maintained during the data collection phase.

Will anyone outside BCH need access to REDCap? ☒ Yes ☐ No ☐ N/A

F. Quality Control Method

To minimize the risk of loss of patient data and maintain data according to institutional guidelines, we will use REDCap™ as the primary receptacle of our data management. REDCap™ is a secure software toolset and workflow methodology for electronic collection and management of research data. Real-time validation rules (with automated data type and range checks) at the time of entry will be incorporated by the BCH team at the time of project development.

Access to the REDCap ™ database will be set during the creation of the project assigning access to only members specified in the CORTICES Registry IRB protocol (BCH: IRB-P00036058) and participating institutions after local IRB and DUA requirements are met and verified by the BCH team. In addition, data collected will be recorded in such a manner (coded) that subjects will not be directly identified. The key code will be stored in a password-protected computer file only accessible internally to research personnel at each internal CORTICES site. All data entered in REDCap will have their own assigned unique study ID per patient and each institution will have a two-digit prefix unique to their site. Information about study

subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

To ensure standardized data entry across sites the team proposing the study will create and share a document called “Data Entry Guide” outlining variable definitions and measurement guidelines. All participating sites are responsible for their own data collection and entry into REDCap using proper methods.

A “beta testing” period with 3-5 institutions (including BCH) will be conducted in order to test REDCap project features such as branching logic, detect errors, and change any variable option before rolling out the study to all sites. Any data entered at the end of the testing period will have to be modified or cleaned according to the latest and final version of the codebook approved by the lead team at BCH and the team proposing the study.

After data entry has been finalized, the research team at BCH will generate individual data cleaning sheets that will be shared to each participating institution to address any missing data point or questionable entry. Each site will have 2 weeks to clean their data queries in order to be added to the final dataset for analysis.

If the analysis will be performed by BCH’s statistician, it will be required to have a Data Analysis Plan document mapping variables and requested tables and graphs prior to analysis. BCH will be in charge of generating the dataset for the BCH statistician or sending the data securely for analysis to other statistician from a CORTICES participating institution.

G. Data Analysis Plan *(Statistician should write this section)*

Patient demographics, injury characteristics, hospital timing factors, and surgical characteristics will be summarized for the cohort. Continuous variables will be presented as means and standard deviations or medians and interquartile ranges, depending on the distribution of the data. Categorical variables will be presented as frequencies and percentages.

The primary aim will estimate the 180-day ED infection proportion in the population. 95% confidence intervals (CIs) for the infection rate will be estimated using the Wilson score method. Infection subtypes (deep vs. superficial), infections requiring IV vs PO antibiotics, and infections requiring surgical washout will similarly be summarized descriptively.

To address the secondary aims, factors associated with 180-day ED infection will first be assessed with univariate tests. Continuous predictors will be compared between infected and non-infected patients using t-tests or Wilcoxon rank sum tests and categorical factors will be evaluated using chi-squared tests or Fisher’s exact tests, as appropriate. Following the univariate comparisons, Multivariable logistic regression will then be used to evaluate the association between the factors from the univariate analyses and 180-day ED infection. Because data will be pooled from multiple institutions, site-level clustering will be accounted for through mixed-effects logistic regression models that include a random intercept for institution to adjust for within-site correlation. Adjusted odds ratios and 95% confidence intervals will be reported.

For the secondary aim evaluating 180-day complications, the complication proportion will be estimated, 95% CIs will be estimated using the Wilson score method.

H. Statistical Power and Sample Size Considerations *(Statistician should write this section)*

Because the primary aim is descriptive, the sample size calculation was based on the secondary aim of comparing time to antibiotic administration between patients who develop a 180-day infection and those who do not. To detect a clinically meaningful difference of 30 minutes in time to antibiotics with 80% power, assuming a standard deviation of 60 minutes, a total sample size of 140 patients (70 patients in each group) is required. The calculation is based on a two-sided, two-sample Wilcoxon rank sum test with a Type I error rate of 0.05.

For multivariable analysis, additional sample size considerations are necessary to ensure adequate power. To detect an odds ratio of 2.0 with 80% power in a logistic regression of 180-day infection on a continuous, normally distributed predictor (e.g. time to antibiotics), while adjusting for covariates, and assuming an R-squared of 0.2 between the predictor of interest and other covariates, 430 patients are required.

I. Study Organization

CORTICES PI: Dr. Kristin Livingston

CORTICES Co-Investigator(s): Dr. Benjamin Shore, Dr. Benjamin Sheffer, Dr. David Spence

CORTICES Coordinator(s): Mackenzie Morris, Libby Szewczak, Saurav Pandey

Statistician: Shanika De Silva

If multicenter, who is lead site?

☐ N/A ☒ BCH ☐ Other, include site name and PI:

J. References

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