Title:
Treatment of fracture-related infection in Latin America. An international Multicenter Study

Principal Investigators	**Date**	**Duration of the project**
Matheus Azi, Guido Carabelli, Carlos Valderrama	7.1.21	24 months

Authors	**Institution/affiliation**
Matheus Azi, Guido Carabelli, Carlos Valderrama	AO Trauma Latin America

Funding agencies
AO Trauma Latin America

Line of research in which the study can be located
Infectious diseases; Trauma

Research question
What are the characteristics of the diagnostic and therapeutic approach for patients with fracture-related infections managed in various centers in Latin America?

Problem formulation
Fracture-related infections represent a frequent complication in the surgical treatment of musculoskeletal trauma, with a variable prevalence according to each segment involved, more frequent in the proximal and distal tibia, calcaneus, patella and pelvis, and acetabulum, and much more frequent in open fractures of any segment.
Diagnosing this pathology is not easy, and recent advances have been made to achieve consensus on definitions, proposing diagnostic algorithms that can help decision-making. The consensus group on fracture-related infections has led most of the recommendations and evidence on this topic in recent years. However, we do not know of work that validates these models in Latin America.
The reality of Latin American countries is complex, with heterogeneous, sometimes inefficient health systems that lead patients with fracture-related infections to chronicity, making treatment more difficult and outcomes less predictable, precisely infection control and functional recovery with reinstatement.
Limited information is available on the outcome of the management of this pathology, in all its stages, from diagnosis to final result, so the purpose of this study is to collect relevant information from patients who present fracture-related infection and describe patterns of diagnosis and treatment, achieving, as far as possible, compare the results with those published in the world literature.

Objectives
General objective
To describe the treatment of fracture-related infections in different institutions in Latin America, emphasizing the diagnostic process and the surgical and medical approach of this type of patient.
Specific objectives
1. To analyze the usefulness of the criteria proposed by the consensus of experts for the diagnosis of fracture-related infections.
2. To describe surgical treatment strategies in patients with fracture-related infections
3. Describe the microbiological profile of fracture-related infections in Latin American centers
4. Explore variables associated with fracture-related infection control outcome
5. Describe strategies for managing soft tissue defects associated with fracture-related infections
6. To describe the quality of life outcomes for people with fracture-related infections

Methodology to use
Type of study: Retrospective cohort observational study
Population (Inclusion/exclusion criteria, if applicable):
Inclusion:
- Adult patients (18 years or older)

- Infection after surgical fracture treatment occurs within the first 90 days after the initial surgery.
- Definitive treatment in one of the centers involved
- Hospital admission from January 1, 2018, to December 31, 2020
- A minimum outpatient follow-up period of one year after the main surgery for the treatment of the infection to evaluate the quality of life and infection control.

Exclusion:
- Incomplete medical records

Variables to evaluate:

The variables will be divided into 12 categories:

Demographics: age, gender, insurance, employment status, weight, and height, among others.

Comorbidity: All the variables that are part of the Charlson Comorbidity Index (Diabetes, acute myocardial infarction, chronic lung disease, dementia, etc.), smoking, anesthetic risk, and history of anti-inflammatory use, among others.

Original trauma: Hospital of the initial treatment, date of the trauma, mechanism of the trauma, polytrauma, transfusions in the original trauma, among others.

Original fracture: Type of fracture (closed or open), classification of the fracture according to the classification of the AO and the classification of Gustilo Anderson, presence of bone or soft tissue defects in the original trauma, among others.

Initial treatment: Type of fixation of the original fracture, use of local antibiotics, use of bone substitutes, dates of surgery, need for soft tissue reconstruction in the original trauma, among others.

Initial infection: Presence of infection in the same hospital episode or readmission for infection, date of diagnosis of infection, confirmatory and suggestive variables proposed by the FRI consensus, presence of systemic inflammatory response syndrome at the time of admission for infection, imaging studies used for diagnosis (radiography, tomography, nuclear medicine, resonance), among others.

Management of the initial infection: Use of antibiotics before surgery, characteristics of the surgeon who performs the first surgical debridement, taking cultures in surgery, use of local antibiotics, and use of negative pressure, among others.

Initial microbiology: Sample origin, isolation bacteria, resistance profile of bacteria, planned for eight different isolates.

Hospitalization initial infection: Antibiotic management of the original infection, adverse reactions to antibiotics, local antibiotics in intermediate surgeries before definitive surgery, among others.

Definitive surgery: Fixation technique used in definitive surgery, use of local antibiotic, use of bone grafts or substitutes, techniques for managing soft tissue defects, among others.

Follow-up: Marital status of the patient at the follow-up appointment, work status, insurer, presence of infectious relapse, and control images, among others.

Hospitalization: Additional episodes after definitive infection management, need for additional surgical procedures, and new microbiological isolations, among others.

Outcomes to evaluate:

- Infectious relapse: Presence of confirmatory or suggestive clinical signs of fracture-related infection, according to the criteria of the FRI consensus, within the first year of follow-up after the main surgery for the treatment of the infection, and that motivates an additional intervention (surgery or additional antibiotics)
- Consolidation: defined as clinical and radiological consolidation. Clinical consolidation – absence of pain on local palpation and loading or walking. Radiological bone union - Presence of bone trabecula in the fracture line in the four cortices of the two standard radiological projections.
- Complications: Defined as any adverse event that requires surgery for treatment. It can be "immediate" (those who needed an additional surgical procedure within up to 30 days of treatment of the infection. For example, hematoma, debridements, change of fixators, change of implant, although partial) or "late" (those that required the surgical procedure after 30 days of definitive treatment. For example, debridement, implant failures, bone grafting).

Information collection process:

The information will be obtained from the medical history of each participating institution and recorded in a database developed specifically for use in multicenter studies.

Proposed statistical analysis: The erroneous h of descriptive statistics will be used, for qualitative variables, absolute and relative frequencies, quantitative variables, measures of central tendency as mean or median, and measures of dispersion as standard deviation or interquartile range, according to the distribution of the variables. Univariate analyses will be performed to explore the relationship of different variables with the risk of infectious relapse, treatment failure, and

amputation, among others. All statistical analyses will be performed in the SPSS Statistics® v20 program (IBM, Chicago, IL).

Analysis plan for each specific objective

Specific objective 1. To analyze the usefulness of the criteria proposed by the consensus of experts for the diagnosis of fracture-related infections.

Analysis plan: It will be defined if the diagnosis of the infection included the confirmatory and/or suggestive criteria proposed by the FRI consensus. The absolute and relative frequency of each of the above criteria shall be described. A multivariate analysis will be performed to explore the association between confirmatory criteria and infection control outcome, defined as the absence of relapse in the first year after definitive surgery to manage the initial infection.

Specific objective 2. To describe surgical treatment strategies in patients with fracture-related infections

Analysis plan: The absolute and relative frequency of each of the strategies used for reconstruction will be described (retention of implants and antibiotics, removal and new internal fixation, removal and external fixation, bone transport, microsurgical flaps, and Masquelet technique, among others). A multivariate analysis will be performed to explore the association between reconstructive strategies and infection control outcome, defined as the absence of relapse in the first year after definitive surgery to manage the initial infection.

Specific objective 3. Describe the microbiological profile of fracture-related infections in Latin American centers

Analysis plan: The absolute and relative frequency of each isolated bacteria, with their resistance profiles, will be described. A multivariate analysis will be performed to explore the association between resistance profile and infection control outcome, defined as the absence of relapse in the first year after definitive surgery for initial infection management.

Specific objective 4. Explore variables associated with fracture-related infection control outcome

Analysis plan: The absolute and relative frequency of each of the variables possibly associated with infection control will be described, including the type of fracture (open vs. closed), bone and associated soft tissue defects, the Charlson Comorbidity Index), bone and soft tissue reconstruction techniques, the time of evolution, among others. A multivariate analysis will be performed to explore the association between these variables and the infection control outcome, defined as the absence of relapse in the first year after definitive surgery to manage the initial infection.

Specific objective 5. Describe strategies for managing soft tissue defects associated with fracture-related infections

Analysis plan: The absolute and relative frequency of each technique used to cover soft defects will be described, as well as who performs the reconstruction (Orthopedic Surgeon vs. Plastic Surgeon), among others. A multivariate analysis will be performed to explore the association between these variables and the infection control outcome, defined as the absence of relapse in the first year after definitive surgery to manage the initial infection.

Specific objective 6. To describe the quality of life outcomes for people with fracture-related infections

Analysis plan: Patients' quality of life will be evaluated with the EuroQol-5D tool at the time of the last follow-up visit, at least one year of follow-up.

Ethical considerations (rating the risk and sustaining it)

This work complies with the standards of research in human beings as provided for in resolution No. 00843 of 1993 of the Ministry of Health and by Decree 309 of 2000 of the Ministry of the Environment. Classifying itself as a risk-free investigation.

It will be submitted for review and approval of the project by the HPTU Research and Research Ethics Committee.

Statistical Analysis Plan

The data will be stored in the server-based database dedicated to the research data storage. The data will be fed by those responsible for each center through a link to access the online form. Only the principal investigator will have access to the information. The structure of the database encodes identification to maintain the confidentiality of the patient's data. Descriptive statistics tools will be used for qualitative variables, absolute and relative frequencies, quantitative variables, measures of central tendency such as mean or median, and measures of dispersion such as standard deviation or interquartile range, according to the distribution of the variables. In addition, univariate analyzes will be performed to explore the relationship of different variables with the risk of infectious relapse, treatment failure, and amputation, among others. All statistical analyzes will be performed in SPSS Statistics® v20 (IBM, Chicago, IL).