THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 |
irb@uab.edu

APPROVAL LETTER

TO: Gelbard, Rondi

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)
IORG Registration # IRB00012550 (IRB 03)

DATE: 29-Apr-2022

RE: IRB-300008650
IRB-300008650-002
Current Practice Patterns in Antibiotic Duration in Necrotizing Soft Tissue Infection: A Surgical Infection Society Multicenter Study

---

The IRB reviewed and approved the Initial Application submitted on 28-Apr-2022 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review:	Exempt
Exempt Categories:	4
Determination:	Exempt
Approval Date:	29-Apr-2022
Approval Period:	No Continuing Review

Documents Included in Review:

- IRB EPORTFOLIO
- IRB PERSONNEL EFORM

To access stamped consent/assent forms (full and expedited protocols only) and/or other approved documents:

1. Open your protocol in IRAP.
2. On the Submissions page, open the submission corresponding to this approval letter. NOTE: The Determination for the submission will be “Approved.”
3. In the list of documents, select and download the desired approved documents. The stamped consent/assent form(s) will be listed with a category of Consent/Assent Document (CF, AF, Info Sheet, Phone Script, etc.)

SIS MULTICENTER STUDY
DATA COLLECTION TOOL

Multicenter Study: Evaluation of Short versus Extended Duration Antibiotic Therapy on Outcomes in Necrotizing Soft Tissue Infection: An SIS Multicenter Study (DATa-NSTI Trial)

Site ID:_____
Enrolling Center: _____
Enrolling Co-investigator: _____

Admission Information
Admitting Service: _____
Patient Number: _____
Date of ED Arrival: _____
Time of ED Arrival: _____
Date of Admission: _____
Time of Admission: _____
Transfer:

Demographics:
Age: _____ Gender:_____ Race:_____ Height (cm): _____ Weight (kg): _____

Comorbidities (Y/N)
Hypertension: ____
Diabetes mellitus: ____ If yes, Type (Insulin-dependent, non-insulin dependent, unsure)
___ With end organ damage
___ Without end organ damage
Peripheral vascular disease: ____
Coronary artery disease: ____
Congestive heart failure ____ If yes, Estimated EF: (55-70%; 40-54%, 35-39%, <35%)
Current smoker: ____
Alcohol abuse: ____
Substance abuse: ____
Chronic pulmonary disease: ____
COPD: ____
On home oxygen: ____
Liters/min ____
History of myocardial infarction: ____
CVA: ____
Dementia: ____
Connective tissue disease: ____
Peptic ulcer disease: ____
Mild liver disease: ____
(without portal hypertension, includes chronic hepatitis)
Moderate or severe liver disease ____
Hemiplegia: ____
Moderate/severe chronic renal disease: ____
Stage I
Stage II
Stage III
Stage IV
Stage V
Prior abdominal operations: ____
Current steroid use: ____
Current chemotherapy: ____
Other immunosuppressants: ____
Tumor without metastases: ____
(exclude if >5 y from diagnosis)
List primary site:
Leukemia (acute or chronic): ____
Lymphoma: ____

Metastatic solid tumor: ____
List primary site:
HIV/AIDS: ____

Pre-existing conditions

Prior NSTI ____
Surgery within 30 days ____
Trauma within 30 days ____
Use of IV drugs ____

Admission physiology

BP: _____ HR: _____ MAP: ____ RR: ____Temp: _____ SpO2:____ FiO2:____
GCS:____ Intubated (Y/N): ____
Vasopressor requirement (Y/N):____
If Yes, circle all that apply:
- Angiotensin III
- Epinephrine
- Norepinephrine
- Phenylephrine
- Vasopressin
- Other: _____

Admission Labs

WBC:	_____ Hospital day Collected:	_____
Hgb:	_____ Hospital day Collected:	_____
Hct:	_____ Hospital day Collected:	_____
Plt:	_____ Hospital day Collected:	_____
INR:	_____ Hospital day Collected:	_____
Tbili:	_____ Hospital day Collected:	_____
Na:	_____ Hospital day Collected:	_____
K:	_____ Hospital day Collected:	_____
Cr:	_____ Hospital day Collected:	_____
Glucose:	_____ Hospital day Collected:	_____
CRP:	_____ Hospital day Collected:	_____
Procalcitonin:	_____ Hospital day Collected:	_____
pH:	_____ Hospital day Collected:	_____
Base Deficit:	_____ Hospital day Collected:	_____
PaO2:	_____ Hospital day Collected:	_____
FiO2:	_____ Hospital day Collected:	_____
MRSA Nare:	_____ Hospital day Collected:	_____

Peak Labs

WBC:	_____ Hospital day Collected:	_____
Hgb:	_____ Hospital day Collected:	_____
Hct:	_____ Hospital day Collected:	_____
Plt:	_____ Hospital day Collected:	_____
INR:	_____ Hospital day Collected:	_____
Tbili:	_____ Hospital day Collected:	_____
Na:	_____ Hospital day Collected:	_____
K:	_____ Hospital day Collected:	_____
Cr:	_____ Hospital day Collected:	_____
Glucose:	_____ Hospital day Collected:	_____
CRP:	_____ Hospital day Collected:	_____
Procalcitonin:	_____ Hospital day Collected:	_____

Radiographic Imaging

XR (Y/N):____
- If Yes, XR Findings:
  - subcutaneous gas
  - other

CT (Y/N):____
- If Yes, CT Findings:
  - subcutaneous gas
  - fat stranding
  - subcutaneous fluid collection
  - subfascial fluid collection
  - subcutaneous edema
  - muscular edema
  - asymmetric fascial thickening
  - increased attenuation of fascia
  - other_____

MR (Y/N):____
- If Yes, MR Findings:

subcutaneous gas
fat stranding
subcutaneous fluid collection
subfascial fluid collection
subcutaneous edema
muscular edema
asymmetric fascial thickening
increased attenuation of fascia
other_____

Operative Variables

Date and Time of Surgical Consult (mm/dd/yyyy, 00:00): _____
Date and Time of first debridement (mm/dd/yyyy, 00:00):_____
Location of Infection (Head/Neck, Upper Extremity, Lower Extremity, Perineum, Abdomen, Chest, Other):
_____
Initial wound size after debridement (in cm^2): _____

Amputation (Y/N): _____
If yes, location: _____
Intraoperative Findings: Well defined subcutaneous fluid collection, Clear involvement of fascia with healthy, viable muscle underneath, Extension of necrosis into muscle and deeper tissue, other: _____
Number of operative debridement:_____
Date and Time of Subsequent Debridement (mm/dd/yyyy, 00:00):
Procedure 1 (mm/dd/yyyy, 00:00):_____
Procedure 2 (mm/dd/yyyy, 00:00):_____
Procedure 3 (mm/dd/yyyy, 00:00):_____
Procedure 4 (mm/dd/yyyy, 00:00):_____
Procedure 5 (mm/dd/yyyy, 00:00):_____

Date and time of final source control procedure (mm/dd/yyyy, 00:00):_____
Final Wound size (in cm^2): _____

Pathology Findings, initial debridement:_____
Pathology Findings, Subsequent debridement:_____
Pathology Findings, Subsequent debridement:_____

Management Variables: Clinical

Infectious Disease Consultation Obtained? (Y/N) If yes, Date: (mm/dd/yyyy):_____
Date of defervescence (mm/dd/yyyy):_____
Date of WBC normalization (mm/dd/yyyy):_____
ICU Supportive therapies (Y/N):
Mechanical Ventilation ____
Total Days ____

Renal Replacement therapy ____
Total Days ____

Vasopressor/inotrope ____
Total Days ____

HBO use ____

Management Variables: Antibiotics and Microbiology

First Dose of Antibiotics (Date and time)_____
Preoperative antibiotics used (Y/N)
Class of preoperative antibiotics (Circle all that apply)
Penicillin
1st generation cephalosporin
2nd generation cephalosporin
3rd generation cephalosporin
4th generation cephalosporin
beta lactam
Fluoroquinolone
Vancomycin
Clindamycin
Macrolide
Aminoglycoside
Flagyl

Tetracycline
Sulfonamide
Pipercillin/tazobactam (Zosyn)
Amoxicillin/clavulanate (Augmentin)
Ampicillin/sulbactam (Unasyn)

Did patient receive IVIG therapy? Y/N

Post-operative antibiotic use (Y/N)
Class of post-intervention antibiotics (Check all that apply):
Penicillin
1st generation cephalosporin
2nd generation cephalosporin
3rd generation cephalosporin
4th generation cephalosporin
beta lactam
Fluoroquinolone
Vancomycin
Clindamycin
Macrolide
Aminoglycoside
Flagyl
Tetracycline
Sulfonamide
Pipercillin/tazobactam (Zosyn)
Amoxicillin/clavulanate (Augmentin)
Ampicillin/sulbactam (Unasyn)

Re-initiation of antibiotics after ≥24hours termination (Y/N): _____
Indication:
worsening physiology
worsening cellulitis
empiric
culture-based
Infection, other than soft tissue
other

Positive Blood Cultures (Y/N):____
If Yes, date and time of first positive blood cultures:_____
If yes, date and time of first negative blood cultures:_____
If yes, list below
Culture 1 Organism _____
Date and time:_____
Resistant Pathogen (Y/N)____
If Yes, describe: _____

Culture 2 Organism _____
Date and time:_____
Resistant Pathogen (Y/N)____
If Yes, describe: _____

Culture 3 Organism _____
Date and time:_____
Resistant Pathogen (Y/N)____
If Yes, describe: _____

Wound cultures obtained (Y/N)____
If yes, list below
Culture 1 Polymicrobial/Monomicrobial
Date and time:_____
Resistant Pathogen (Y/N)____
If Yes, describe: _____

Culture 2 Polymicrobial/Monomicrobial
Date and time:_____
Resistant Pathogen (Y/N)____
If Yes, describe: _____

Culture 3 Polymicrobial/Monomicrobial

Date and time:_____
Resistant Pathogen (Y/N)____
If Yes, describe: _____

Bone Biopsy obtained (Y/N)
If yes, list below
Culture Organism _____
Date and time:_____
Resistant Pathogen (Y/N)____
If Yes, describe: _____

Outcomes: Initial
Date and time of discharge (mm/dd/yyyy, 00:00):_____
Discharge Status (Living, In-Hospital Death): _____
If In-Hospital death, time to occurrence (hours):_____
If Living discharge, time to discharge (hours): _____
Time from final intervention to discharge (hours): _____
Location of Death (ED,OR, ICU, Floor, Hospice): _____

Complications: (check all that apply)
_____ Pneumonia
_____ ARDS
_____ Sepsis
_____ Acute Kidney Injury
If yes, Stage_____
_____ DVT/PE
_____ Clostridium Difficile Infection
_____ Unplanned Return to OR
Other: _____

Hospital LOS (days): _____
ICU LOS (days): _____
Mechanical ventilation (days) _____

Outcomes: 30 Day
All Cause Re-admission (Y/N):____
If Yes, Date and Time: (mm/dd/yyyy, 00:00):_____
NSTI related re-admission (Y/N): ____
If Yes, Date and Time: (mm/dd/yyyy, 00:00):_____
Mortality (Y/N):____

Site ID	Each site's assigned number
	Admission Information
Admitting Service	Service to which the patient is admitted (Surgical, Internal Medicine, Other)
Patient Number	6-digit number starting with your Site ID, ie. 12-001, 12-002, 12-003, and 12-004.
Date of ED Arrival	Date of Arrival to Emergency Department (mm/dd/yyyy)
Time of ED Arrival	Time of Arrival to Emergency department (military)
Date of Admission	Date of Hospital Admission (mm/dd/yyyy)
Time of Admission	Time of hospital admission (military)
Transfer	Patient was transferred from outside institution
Demographics	
Age	Age of patient enrolled at time of admission
Gender	Gender of patient enrolled
Race	Racial Categories (per NIH OMB Standards): American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander White
Height	Height of patient in centimeters
Weight	Weight of patient in kilograms
Comorbidities	
HTN	History of hypertension/Abnormally high blood pressure
Diabetes	A long-term metabolic disorder characterized by high blood sugar, insulin resistance, and relative lack of insulin * Insulin-dependent indicates daily use of insulin injection for glucose control. * Non-insulin dependent indicates use of oral medications and/or diet modification for glucose control. * Specify with or without end organ damage ((retinopathy, neuropathy, or brittle diabetes)
PVD	History of Peripheral Vascular Disease – A circulation disorder characterized by narrowing or blockage of the blood vessels; Abdominal aortic aneurysm is an enlargement of the abdominal portion of the aorta or main blood vessel that delivers blood to the body and is measured at its greatest diameter in cm
Coronary artery disease	An impedance or blockage of one or more blood vessels that supplies blood to the heart
MI	History of definite or probable Myocardial Infarction (EKG changes and/or enzyme changes)
CHF	A chronic and progressive condition in which the heart is inefficient atpumping blood and oxygen to meet the body's demands Indicate estimated ejection fraction (EF) based on a recent echocardiogram measurement expressed as a percentage of how much blood the left ventricle pumps out with each contraction.
Current Smoker	If patient is an active smoker at the time of initial presentation, check yes
Alcohol abuse	A pattern of drinking that results in harm to one's health, interpersonal relationships, or ability to work
Substance abuse	The harmful or hazardous use of psychoactivesubstances, including illicit drugs
Recent IV drug Use	Intravenous administration of psychoactivesubstances, including illicit drugs within the past 30 days

COPD	Any long-term lung disorder that affects airways, lung tissues or circulation of blood into and out of the lungs. The most common disorders include asthma, COPD, emphysema, interstitial lung disease, pulmonary hypertension, cystic fibrosis, chronic pneumonia
On home oxygen	Current use of supplemental oxygen at home usually administered via nasal cannula which flows at a rate of L/min
CVA/TIA	Impaired or blocked blood flow to the brain due to a blockage or artery rupture resulting in death of brain cells due to lack of oxygen resulting in numbness, weakness on one side of the body and slurred speech. These symptoms improve and do not significantly impair activities of daily living; Transient ischemic attack is a CVA that only lasts a few minutes.
Hemiplegia	Presence of residual paralysis of one side of the body
Dementia	An overall term that describes cognitive decline including worsening memory, language, problem-solving and other thinking skills. Common conditions including Alzheimer's disease, vascular dementia.
Connective tissue disease	Any disorder that involves the protein-rich tissue (fat, bone, cartilage) that supports organs and parts of the body usually the joints, muscles and skin.
Peptic ulcer disease	History of treatment for ulcer disease or history of bleeding ulcer. Sores or ulcers in the stomach or first portion of the intestine (duodenum)
Liver Disease	Mild liver disease (without portal HTN, Liver dysfunction due to inflammation that does not result in fibrosis includes chronic hepatitis) Moderate or severe liver disease Liver dysfunction that has progressed to fibrosis and/or cirrhosis with associated findings such as portal hypertension, ascites, varices
CKD	History of moderate to severe Chronic Kidney Disease. Chronic kidney dysfunction with a decreased GFR (<45) ranging to renal failure (ESRD) with need for dialysis
Current steroid use	Current use of any steroid medication
Current chemotherapy	Currently on chemotherapy for any reason
Other immunosuppressants	List other immunosuppressive medications not listed above
Tumor without metastases	Any cancer that is localized and has not spread to other parts of the body (excludes if >5 yr from diagnosis)
Metastatic solid tumor	Any cancer that has spread to other parts of the body
Leukemia	A cancer of the blood or bone marrow
Lymphoma	A cancer of the immune or lymphatic system which affects cells of the lymph nodes, spleen, thymus, bone marrow
HIV/AIDS	Human immunodeficiency virus (HIV) damages the immune system which can develop into acquired immunodeficiency syndrome (AIDS) which is a condition in which progressive failure of the immune system allows life-threatening infections and cancers to thrive

Pre-existing conditions	
Prior NSTI	Patient with a prior medical history of a necrotizing soft tissue infection requiring surgical debridement.
Surgery within 30 days	Patient underwent operative procedure within the past 30 days.
Trauma within 30 days	Patient was involved in a traumatic mechanism requiring evaluation by emergency department within the past 30 days.
Admission physiology	
BP	First Blood Pressure (mmHg)
HR	Heart rate at the time of presentation (BPM)
MAP	First Mean Arterial Pressure (mmHg)
RR	First Respiratory rate
Temp	Temperature at the time of presentation (Celsius)
SpO2	First Oxygen saturation
FiO2	Fraction of Inspired Oxygen at time of first oxygen saturation
GCS	First Glascow Coma Scale score Best eye response (4) No eye opening Eye opening to pain Eye opening to sound Eyes open spontaneously Best verbal response (5) No verbal response Incomprehensible sounds Inappropriate words Confused Orientated Best motor response (6) No motor response. Abnormal extension to pain Abnormal flexion to pain Withdrawal from pain Localizing pain Obeys commands
Intubated	Patient intubated pre-hospital or required intubation in Emergency Department
Vasopressors	Patient required vasopressors pre-hospital or required pressors in Emergency Department
	List name of pressors (in generic form) Angiotensin II Epinephrine Norepinephrine Phenylephrine Vasopressin Other: _____
Laboratory Values - Admission	
WBC	First white blood cell count (10^3/uL)
HGB	First hemoglobin (g/dL)
HCT	First hematocrit (%)
PLT	First Platelet (10^3/uL)
INR	First International Normalized Ratio

Na	First Sodium (mEq/L)
K	First Potassium (mEq/L)
Cr	First Creatinine (umol/L)
Glucose	First Glucose (mg/dL)
Total Bilirubin	First Bilirubin (mg/dL)
CRP	First C-Reactive Protein (mg/dL)
pH	First pH value (arterial preferred, but venous value acceptable if no arterial value available)
Base Deficit	First Deficit of base on arterial blood gas (mEq/L)
PaO2	First partial pressure of oxygen (mmHg) – arterial only
FiO2	Fraction of Inspired Oxygen at time of first PaO2
Laboratory Values - Peak	
WBC	Highest white blood cell count (10^3/uL)
HGB	Highest hemoglobin (g/dL)
HCT	Highest hematocrit (%)
PLT	Highest Platelet (10^3/uL)
INR	Highest International Normalized Ratio
Na	Highest Sodium (mEq/L)
K	Highest Potassium (mEq/L)
Cr	Highest Creatinine (umol/L)
Glucose	Highest Glucose (mg/dL)
Total Bilirubin	Highest Bilirubin (mg/dL)
CRP	Highest C-Reactive Protein (mg/dL)
Radiographic Imaging	
XR	Radiographs obtained prior to OR and their findings (subcutaneous gas, other)
CT	Computed Tomography obtained prior to OR and its findings (subcutaneous gas,fat stranding, subcutaneous fluid collection, subfascial fluid collection, subcutaneous edema, muscular edema, asymmetric fascial thickening, increased attenuation of fascia, other)
MR	Magnetic resonance imaging obtained prior to OR and its findings (subcutaneous gas,fat stranding, subcutaneous fluid collection, subfascial fluid collection, subcutaneous edema, muscular edema, asymmetric fascial thickening, increased attenuation of fascia, other)
Operative Variables	
Date and time of surgical consult	mm/dd/yyyy, 00:00 (military)
Date and time of First debridement	Time of incision of first debridement, mm/dd/yyyy, 00:00 (military)
Time to initial debridement	Duration of time from surgical consult to initial debridement, in minutes
Location of Infection	Main site in which the infection is present, if multiple, circle all that apply. Head/Neck, Upper Extremity, Lower Extremity, Perineum, Abdomen, Chest, Other
Wound size after initial debridement	Measurements of wound after initial debridement, in cm^2
Amputation	Did patient require amputation during this admission? If yes, level of amputation.
Intraoperative Findings	Operative Findings on initial debridement. Well defined subcutaneous fluid collection, Clear involvement of fascia with healthy, viable muscle underneath, Extension of necrosis into muscle and deeper tissue, other
Number of operative debridements	Total number of debridements required to obtain source control, including initial
Date and Time of subsequent debridements	List each operative intervention prior to source control, mm/dd/yyyy, 00:00 (military)

Date and time of final source control procedure	List the final source control procedure as determined by the managing surgeon, mm/dd/yyyy, 00:00 (military). If patient was initially declared to have source control and required subsequent debridements after >48hours, this will be listed under complications
Final wound size	Measurements of wound after final source control procedure, in cm^2
Pathology Findings	
Initial Debridement	List the pathology findings for first surgical debridement
Subsequent Debridement	List the pathology findings for subsequent debridements, when applicable
Clinical Management Variables	
Infectious Disease Consultation	Was an infectious disease physician consulted, if so date of consultation. mm/dd/yyyy
Date of defervescence	First date in which patient has a temperature <38.6 for ≥24 hours, mm/dd/yyyy
Date of WBC normalization	First date in which patient has normalization of white blood cell count, as defined by individual institution laboratory values, mm/dd/yyyy
ICU Supportive therapies	Did the patient undergo the following supportive therapies in the ICU? If yes, list total number of days of therapy.
HBO Use	Did the patient undergo hyperbaric oxygen therapy? (Yes/No)
Antibiotics and Microbiology	
First dose of antibiotics	List the date and time of first dose of antibiotics, mm/dd/yyyy, 00:00 (military).
Preoperative Antibiotics	Did the patient receive antibiotics prior to surgery? Yes/No If yes, circle all that apply.
Class of preoperative antibiotic	Penicillin 1st generation cephalosporin 2nd generation cephalosporin 3rd generation cephalosporin 4th generation cephalosporin beta lactam Fluoroquinolone Vancomycin Clindamycin Macrolide Aminoglycoside Flagyl Tetracycline Sulfonamide Pipercillin/tazobactam (Zosyn) Amoxicillin/clavulanate (Augmentin) Ampicillin/sulbactam (Unasyn)
IVIG therapy	Did the patient receive a dose of immunoglobulin therapy? Yes/No
Post-operative antibiotics	Did the patient receive antibiotics after initial debridement? Yes/No
Class of post-operative antibiotics	Circle all antibiotics that the patient received. Include Total duration received and start date/time, mm/dd/yyyy, 00:00 (military). Penicillin 1st generation cephalosporin 2nd generation cephalosporin 3rd generation cephalosporin 4th generation cephalosporin

	beta lactam Fluoroquinolone Vancomycin Clindamycin Macrolide Aminoglycoside Flagyl Tetracycline Sulfonamide Pipercillin/tazobactam (Zosyn) Amoxicillin/clavulanate (Augmentin) Ampicillin/sulbactam (Unasyn)
Re-initiation of antibiotics after ≥24hours termination	Did the patient require antibiotics >24hours after decision to terminate antibiotic therapy? Yes/No
Indication for	Please list indication for re-initiation of antibiotics: (worsening physiology, worsening cellulitis, empiric, culture-based, Infection other than soft-tissue, other)
Positive Blood cultures	Any pathogen present in paired blood culture sets of >105(per CLSI standard), exclusive of contaminant organisms.
If yes, List date and time of first positive blood culture	List the date and time the positive blood culture was drawn, mm/dd/yyyy, 00:00 (military).
If yes, List date and time of first negative blood culture after positive culture	List the date and time the negative blood culture was drawn, mm/dd/yyyy, 00:00 (military).
If yes, list below	List organism name to include genus and species, date and time of culture mm/dd/yyyy, 00:00 (military)
Resistant pathogen	Any of the 13 antibiotic resistant phenotypes as defined by the CDC: Methicillin-resistant Staphylococcus aureus, Carbapenem-resistant Enterobacterales, Carbapenem-resistant E. coli, Carbapenem-resistant Enterobacter spp., Carbapenem-resistant Klebsiella aerogenes/ oxytoca/pneumonia, Extended-spectrum cephalosporin-resistant E. coli, Extended-spectrum cephalosporin-resistant Klebsiella oxytoca /pneumonia, Carbapenem-non-susceptible Pseudomonas Aeruginosa, Multidrug-resistant Pseudomonas Aeruginosa, Carbapenem-non-susceptible Acinetobacter spp, Multidrug-resistant Acinetobacter spp., Vancomycin-resistant Enterococcus faecalis, Vancomycin-resistant Enterococcus faecium
Wound cultures obtained	Were wound cultures obtained intraoperatively? Yes/No
If yes, list below	List organism name to include genus and species, date and time of culture mm/dd/yyyy, 00:00 (military)
Resistant pathogen	Any of the 13 antibiotic resistant phenotypes as defined by the CDC: Methicillin-resistant Staphylococcus aureus, Carbapenem-resistant Enterobacterales, Carbapenem-resistant E. coli, Carbapenem-resistant Enterobacter spp., Carbapenem-resistant Klebsiella aerogenes/ oxytoca/pneumonia, Extended-spectrum cephalosporin-resistant E. coli, Extended-spectrum cephalosporin-resistant Klebsiella oxytoca /pneumonia, Carbapenem-non-susceptible Pseudomonas Aeruginosa, Multidrug-resistant Pseudomonas Aeruginosa, Carbapenem-non-susceptible Acinetobacter spp, Multidrug-resistant Acinetobacter spp., Vancomycin-resistant Enterococcus faecalis, Vancomycin-resistant Enterococcus faecium
Bone Biopsy Obtained	Was a bone biopsy obtained intraoperatively or under sterile conditions (by Interventional radiology)? Yes/No
If yes, list below	List organism name to include genus and species, date and time of culture mm/dd/yyyy, 00:00 (military)

Resistant pathogen	Any of the 13 antibiotic resistant phenotypes as defined by the CDC: Methicillin-resistant Staphylococcus aureus, Carbapenem-resistant Enterobacterales, Carbapenem-resistant E. coli, Carbapenem-resistant Enterobacter spp., Carbapenem-resistant Klebsiella aerogenes/ oxytoca/pneumonia, Extended-spectrum cephalosporin-resistant E. coli, Extended-spectrum cephalosporin-resistant Klebsiella oxytoca /pneumonia, Carbapenem-non-susceptible Pseudomonas Aeruginosa, Multidrug-resistant Pseudomonas Aeruginosa, Carbapenem-non-susceptible Acinetobacter spp, Multidrug-resistant Acinetobacter spp., Vancomycin-resistant Enterococcus faecalis, Vancomycin-resistant Enterococcus faecium
Initial Outcomes	
Date and Time of Discharge	Date and time of patient discharge or death, mm/dd/yyyy, 00:00 (military)
Discharge status	Status of patient at discharge. Options include living and in-hospital death
If In-Hospital death, time to occurrence	Time from admission to time of death (in hours)
Location of death	If in-hospital death, location. Options include ED, OR, ICU, Floor, Hospice
If living discharge, time to discharge	Time from admission to time of discharge (in hours)
Time from final intervention to discharge	Time from final source control procedure to discharge (in hours)
Complications (Check all that apply)	Defined by the National Trauma Databank
Pneumonia	Check if pneumonia reported during patient's hospital course, as defined by NSQIP case must meet Radiology (A) criteria AND ONE of the following TWO Signs/Symptoms/Laboratory (B) scenarios as listed below within the 30 days after the principal operative procedure. Radiology: ONE chest radiological exam (x-ray or CT)* demonstrating at least ONE of the following: Infiltrate, Consolidation, Opacity, Cavitation, Pneumonia, possible, probable, suspicious for pneumonia OR A diagnosis of pneumonia is rendered by a physician or advanced practitioner based on the findings demonstrated on a chest radiological exam (x-ray or CT). *Two imaging tests are required for patients with underlying pulmonary or cardiac disease (e.g., respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease). Signs/Symptoms/Laboratory: SCENARIO #1 At least ONE of the following: Fever (>38°C or >100.4°F) with no other recognized cause Leukopenia (<4000 WBC/mm3) or leukocytosis 12,000 WBC/mm3) For adults ≥ 70 years old, altered mental status with no other recognized cause AND At least ONE of the following: 5% Bronchoalveolar lavage (BAL) -obtained cells contain intracellular bacteria on direct microscopic exam (e.g., Gram stain) Positive growth in blood culture not related to another source of infection, Positive growth in culture of pleural fluid, Positive quantitative culture from minimally contaminated lower respiratory tract (LRT) specimen (e.g. BAL or protected specimen brushing) OR, SCENARIO #2 At least ONE of the following: Fever (>38°C or >100.4°F) with no other recognized cause Leukopenia (<4000 WBC/mm3) or leukocytosis (≥12,000 WBC/mm3) For adults ≥ 70 years old, altered mental status with no other recognized cause AND At least TWO of the following: New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements, New onset or worsening cough, dyspnea or tachypnea, Rales (crackles) or rhonchi, Worsening gas exchange (e.g. O2 desaturations (e.g., PaO2/FiO2 ≤ 240), increased oxygen requirements, or increased ventilator demand)

<table>
<tr><td>ARDS</td><td>Check if ARDS reported during patient’s hospital course. Defined as, within 1 week of known clinical insult or new or worsening respiratory symptoms. Chest imaging: Bilateral opacities – not fully explained by effusions, lobar/lung collage, or nodules
Origin of edema: Respiratory failure not fully explained by cardiac failure of fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present. Oxygenation: Mild 200 mm Hg < PaO2/FIO2 < 300 mm Hg With PEEP or CPAP >= 5 cm H2Oc, Moderate 100 mm Hg < PaO2/FIO2 < 200 mm Hg With PEEP >5 cm H2O, Severe PaO2/FIO2 < 100 mm Hg With PEEP or CPAP >5 cm H2O</td></tr>
<tr><td>Sepsis</td><td>Check if Sepsis reported during patient’s hospital course, defined by Severe sepsis: sepsis plus organ dysfunction, hypotension (low blood pressure), or hypoperfusion (insufficient blood flow) to 1 or more organs. Septic shock: sepsis with persisting arterial hypotension or hypoperfusion despite adequate fluid resuscitation.
Must have occurred during the patient's initial stay at your hospital.
A diagnosis of sepsis must be documented in the patient's medical record. Consistent with the American College of Chest Physicians and the Society of Critical Care Medicine October 2010</td></tr>
<tr><td>Acute Renal Failure</td><td>Acute Kidney Injury as defined by 2012 KDIGO Clinical Practice Guideline
Table 2 | Staging of AKI
<table><tr><th>Stage</th><th>Serum creatinine</th><th>Urine output</th></tr><tr><td>1</td><td>1.5–1.9 times baseline
OR
⩾0.3 mg/dl (⩾26.5 μmol/l) increase</td><td><0.5 ml/kg/h for 6–12 hours</td></tr><tr><td>2</td><td>2.0–2.9 times baseline</td><td><0.5 ml/kg/h for ⩾12 hours</td></tr><tr><td>3</td><td>3.0 times baseline
OR
Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 μmol/l)
OR
Initiation of renal replacement therapy
OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2</td><td><0.3 ml/kg/h for ⩾24 hours
OR
Anuria for ⩾12 hours</td></tr></table></td></tr>
<tr><td>DVT/PE</td><td>Check if DVT/PE reported during patient’s hospital course.
DVT = Deep Vein Thrombosis, PE = Pulmonary embolism.
must have occurred during the patient's initial stay at your hospital.
The patient must be treated with anticoagulation therapy and/or placement of a vena cava filter or clipping of the vena cava.
A diagnosis of DVT must be documented in the patient's medical record, which may be confirmed by venogram, ultrasound, or CT.
A lodging of a blood clot in a pulmonary artery with subsequent obstruction of blood supply to the lung parenchyma. The blood clots usually originate from the deep leg veins or the pelvic venous system.
Must have occurred during the patient's initial stay at your hospital.
Consider the condition present if the patient has a V-Q scan interpreted as high probability of pulmonary embolism or a positive pulmonary arteriogram or positive CT angiogram and/or a diagnosis of PE is documented in the patient’s medical record. Exclude subsegmental PEs.</td></tr>
<tr><td>Clostridium Difficile Infection</td><td>Patient tested positive for clostridium difficile via C. difficile toxin assay or C. difficile nucleic acid amplification assay</td></tr>
</table>

Unplanned Return to OR	Check if Unplanned Return to OR reported during patient's hospital course. Free text entry, explain reasons for return, defined by Patients with an unplanned operative procedure OR patients returned to the operating room after initial operation management of a related previous procedure. Must have occurred during the patient's initial stay at your hospital. EXCLUDE: Pre-planned, staged and/or procedures for incidental findings. EXCLUDE: Operative management related to a procedure that was initially performed prior to arrival at your center.
Hospital LOS (days)	Free text entry for number of consecutive days patient hospitalized at initial admission (Day of admission = hospital day #1) LOS = Length of Stay The cumulative amount of time spent in the Hospital. Each partial or full day should be measured as one calendar day.
ICU LOS	Free text entry of number of consecutive days patient required ICU admission (ICU = Intensive Care Unit, LOS = Length of Stay) - Day of admission = hospital day #1 The cumulative amount of time spent in the ICU. Each partial or full day should be measured as one calendar day.
30 Day Outcomes	
All Cause Readmission	Patient readmission within 30 days, regardless of cause. If Yes, date and time mm/dd/yyyy, 00:00 (military)
NSTI-related re-admission	Patient readmission within 30 days, due to necrotizing soft tissue infection. If Yes, date and time mm/dd/yyyy, 00:00 (military)
Mortality	Death within 30 days, regardless of cause. If Yes, date and time mm/dd/yyyy, 00:00 (military)

Evaluation of Short versus Extended Duration Antibiotic Therapy on Outcomes in Necrotizing Soft Tissue Infection: An SIS Multicenter Study (DATa-NSTI Trial)

Sabrina Goddard, MD
Physician, Surgery, Trauma and Acute Care
University of Alabama Birmingham

Rondi Gelbard, MD
Physician, Surgery, Trauma and Acute Care
University of Alabama Birmingham

Table of Contents:

I. Investigators and Study Personnel

Primary Investigators

Sabrina Goddard, MD
Physician, Surgery, Trauma and Acute Care
University of Alabama Birmingham

Rondi Gelbard, MD
Physician, Surgery, Trauma and Acute Care
University of Alabama Birmingham

Co-Investigators

Zain Hashmi, MD
Physician, Surgery, Trauma and Acute Care
University of Alabama Birmingham

Jonathan Black, MD
Physician, Surgery, Trauma and Acute Care
University of Alabama Birmingham

Jan Jansen, MD
Physician, Surgery, Trauma and Acute Care
University of Alabama Birmingham

Russell Griffin, PhD
Epidemiology
University of Alabama Birmingham

Study Personnel

Biostatistical support from UAB Department of Surgery
Clinical research support from UAB Department of Surgery

II. Background

Necrotizing soft tissue infections (NSTI) are severe, rapidly spreading infections of the soft tissue and fascia with high morbidity and a historic high mortality. The incidence of necrotizing soft tissue infections is thought to be around 30,000 based on recent studies of the National Inpatient Sample (1,2).Mortality for NSTI has been reported as high as 34% (3,4) but more recently has declined to 10-14% (5). There is also substantial healthcare system burden with a readmission rate estimated at approximately 24-29% (1,2).

NSTI is an inclusive term intended to describe all infections with a necrotizing component involving any or all the layers of the soft tissue compartment, from the superficial dermis and subcutaneous tissue to the deeper fascia and muscle. The clinical manifestations range from pyoderma to necrotizing cellulitis, myositis, progressive bacterial synergistic gangrene, and necrotizing fasciitis (7). NSTI can be caused by polymicrobial (Type I) or monomicrobial organisms (Type II). Other less common organisms, including clostridium and gram-negative marine organisms account for a third type of NSTI (8,9). Regardless of the type, patients can present with a wide range of clinical findings and having a high index of suspicion is essential for early diagnosis and management.

The mainstay of treatment is early and aggressive surgical debridement of infected and necrotic tissue. Early diagnosis and intervention are the only consistently proven predictors of outcome for NSTI. In a recent EAST PMG, they found an overall mortality rate of 14% in the early intervention group versus 25.8% in the late intervention group (5).

Though most would agree that initiation of broad-spectrum antibiotics and rapid surgical intervention are paramount – there is no consensus regarding duration of antibiotic therapy after source control. Current guidelines are based on retrospective, small population studies as well as expert consensus and derivations from similar infections.These guidelines suggest that broad-spectrum antibiotics including gram-negative, gram-positive and anaerobic coverage be initiated immediately after the diagnosis is suspected and continued until adequate source control is achieved (7, 10,11). The 2014 IDSA guidelines recommend “In the absence of definitive clinical trials, antimicrobial therapy should be administered until further debridement is no longer necessary, the patient has improved clinically, and fever has been absent for 48–72 hours” (11). While the 2020 SIS updated guidelines state “Shorter course antimicrobial therapy (<7 days) appears equivalent to longer therapy and should be considered” (10).A multi-center study in 2016 showed significant antibiotic variation between high-volume NSTI centers (6). This further highlights how little is known about best care practices for patients with NSTI and thusly the heterogenous practice patterns. Because of this, it is not uncommon for antibiotics to be continued for a prolonged period of time, well beyond the final surgical debridement.

It is well established that shorter course antibiotics reduce the risk of antimicrobial resistance and the development of clostridium difficile colitis (11). However, under-treatment may place the patient at risk for recurrent infection, increased length of stay, and mortality. Therefore, determining an ideal duration of antibiotic therapy inpatients with necrotizing soft tissue infections may help to mitigate these risks. Recent studies such as the STOPIT trial have found that a shortened course of antibiotics (4 days) for intra-abdominal infections is equivalent to an extended course past the resolution of physiologic abnormalities (12). Lauerman et al performed a retrospective review of 168 patients with Fournier’s gangrene in 2017 and found no difference in mortality with a shorter course of antibiotic therapy of 7 days or less, with a mean antibiotic duration of 4.8 days from final wound management (13). In 2021, Valadez et al performed a

retrospective review of 142 patients which showed no significant difference in in-hospital mortality or 30-day readmission with an antibiotic course of 7 days or less (14).

The 2020 Surgical Infection Society (SIS) Updated Guidelines on the Management of Complicated Skin and Soft Tissue Infections states that “shorter course antimicrobial therapy (<7days) appears equivalent to longer therapy and should be considered”. However, this is a weak recommendation based on moderate quality evidence. The guideline also states that there is a need for further prospective evaluation into the duration of antimicrobial agents in necrotizing infections (10). Furthermore, a recent survey of the SIS membership using a modified Delphi identified treatment duration for NSTI as one of the top three topics for further research (15). Which has led to this proposal for a multicenter prospective observational study regarding short versus long antibiotic duration in NSTI.

III. Aims, Hypothesis, and Outcomes

Aims:

1. To determine if patients with NSTI who receive short course antibiotic therapy (<7 days after final source control procedure) have similar 30-day mortality compared to those patients who receive a longer duration of antibiotics (≥7 days after final source control procedure)
2. To determine the effect of short versus long course antibiotics on postoperative outcomes including complications, length of stay, and readmissions.
3. To describe current practices regarding duration and appropriateness of antimicrobial therapy for patients undergoing surgical debridement for confirmed necrotizing soft tissue infection

Hypothesis:

Null Hypothesis (Ho) - Short-term antimicrobials (<7 days after final source control procedure) for Necrotizing Soft Tissue Infection are inferior to long-term (≥7 days after final source control procedure) antimicrobial courses in regards to mortality by the non-inferiority margin (Δ) of 7%

Primary Outcome:

30 day Mortality

Secondary Outcomes:

Hospital and ICU length of stay

30-day readmission

Duration of antibiotic therapy

Antimicrobial-free days at 30 days

Recurrent Infection

(defined as worsening clinical status requiring additional debridement within 30 days of admission)

IV. Study Methods

The study will be a multicenter, prospective, observational cohort study to evaluate clinical outcomes of patients who received short-term versus long-term antibiotic therapy after source control. The study groups will be decided based on the duration of antimicrobial therapy, patients who received a short course of antibiotic therapy "ShortDur Group" (<7 days after final source control procedure) will be compared to patients receiving an extended course of antibiotic therapy "ExtDur Group" (≥7 days after final source control procedure).

This study will prospectively collection patient information for two years from September 1, 2022 up to September 30, 2024 until the sample size is collected. Patients will be enrolled from multiple centers throughout the United States and internationally. Demographic data, as well as laboratory values, radiographic findings, intra-operative management, pathology, microbiology results, antibiotic duration and type, complications and other clinical outcomes will be collected on all patients.

This study will define NSTI as skin and soft tissue infection requiring surgical debridement with evidence of necrotic skin, soft tissue, fascia, or muscle. Source control will be defined as any procedure that stops the ongoing contamination of the wound and removes the majority of the contaminated/necrotic tissue to the extent that no further acute interventions are felt to be necessary. Depending on the site and origin of the infection, multiple techniques can be utilized to obtain source control, including incision and debridement, wide local excision, as well as amputation. The adequacy of source control for any given patient will be determined by the operating surgeon.

Inclusion Criteria:

Patients > 18 years of age

Patient admitted to hospital with surgically confirmed necrotizing soft tissue infection (See definition above)

Patients receiving a minimum of 24 hours of antibiotics

Survival at least 7 days from source control procedure

Exclusion Criteria:

Patients <18 years of age

Patients with non-necrotizing soft tissue infection

Patients who did not undergo surgical debridement

Pregnant Patients

Incarcerated Patients

Patients who underwent surgical debridement at an outside facility

Intervention:

There will be no interventions solely for the purpose of this study. Care will be at the discretion of the local surgical team.

Consent Procedures:

This is a prospective observational study, designed to prospectively record data on patients who are managed according to institutional patient management protocols. Thus, waiver of informed consent is requested. Data will be recorded on a data sheet and transferred to a secured database that is devoid of patient identifiers.

Risk/Benefit Analysis:

This study involves no more than minimal risk to patients, as it is an observational study. A potential risk is a breach of confidentiality. There is a potential future benefit if we define optimal duration of antibiotic therapy in patients with necrotizing soft tissue infection. This would help to minimize the complications associated with unnecessary antibiotics including clostridium difficile colitis and antimicrobial resistance.

V. Data Collection

Data will be abstracted from the available electronic medical record and put directly into the Redcap database. A complete description of the data points is available (see Data Collection Sheet, Appendix). Data will include basic demographic information, documented co-morbidities, admission severity of illness, microbiology data, operative variables, primary and secondary endpoints, along with additional other clinical, confounding, or hospital course variables. Data collection will start at the coordinating site once IRB approval is obtained. Once the other sites obtain IRB approval and a data use agreement is in place, then data collection can be initiated.

VI. Data Analysis

Sample Size required/Justification of sample size

We sought to determine equivalence between short duration and extended duration antibiotic groups, based on Aim one outcome of mortality, based on a known 14% mortality. We assumed a 50/50 split of ShortDur Group and ExtDur Group. We calculated that a sample size of 311 patients per group would be required to give the study 80% power to exclude a difference in mortality rate of greater than 7% between the two groups, at an alpha level of 0.05.

Recruitment will stop when 742 participants are enrolled to yield 622 evaluable subjects, assuming a 20% attrition or loss to follow-up

Study Duration, Enrollment, Number of Sites:

Given that this is an observational multicentre study, we anticipate enrolling 742 patients from 25-30 national and international sites over a two year period. This would equate to roughly 15 patients per year per center. This appears consistent with prior single-center annual NSTI capture data (6, 16-20).

Statistical Analysis Plan:

Patients having a necrotizing soft tissue infection as defined below will be identified by the local study investigators. Within 72 hours of the initial intervention, the local investigator will review criteria for enrollment. Study data will be collected and managed using REDCap electronic data capture tools hosted at the University of Alabama Birmingham. All participating sites will be instructed to record data elements onto the case report form (CRF) only as specifically documented in the medical record or examined by the clinician. If a data element is not recorded in the medical record, then it is left blank on the CRF and recorded as “missing”. Missing items will be excluded from data analysis.

Continuous data will be reported as means +/- standard deviation or median (interquartile range) for nonparametric distributions and compared with T-test or Mann-Whitney U test as appropriate. Based on final diagnosis, subjects will be categorized into short term versus extended duration antibiotics. Comparisons between groups will be performed using analysis of variance, chi-squared test, and Kruskall-Wallace test. Counts were reported as frequencies and compared with chi-squared test. A p-value of <0.05 will be considered statistically significant. Statistical analyses will be performed using Stata.

XI. References

1. *Collins CM, McCarty A, Jalilvand A, et al. Outcomes of Patients with Necrotizing Soft Tissue Infections: A Propensity-Matched Analysis Using the National Inpatient Sample. Surg Infect (Larchmt). 2022*
2. *May AK, Talisa VB, Wilfret DA, et al. Estimating the Impact of Necrotizing Soft Tissue Infections in the United States: Incidence and Re-Admissions. Surg Infect (Larchmt). 2021*
3. McHenry, C. R., Piotrowski, J. J., Petrinic, D., & Malangoni, M. A. (1995). Determinants of mortality for necrotizing soft-tissue infections. Annals of surgery
4. George, S. M., Harrison, D. A., Welch, C. A., Nolan, K. M., & Friedmann, P. S. (2008). Dermatological conditions in intensive care: a secondary analysis of the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme database. Critical care (London, England)
5. Gelbard, R. B., Ferrada, P., Yeh, D. D., Williams, B. H., Loor, M., Yon, J., Mentzer, C., Khwaja, K., Khan, M. A., Kohli, A., Bulger, E. M., & Robinson, B. (2018). Optimal timing of initial debridement for necrotizing soft tissue infection: A Practice Management Guideline from the Eastern Association for the Surgery of Trauma. The journal of trauma and acute care surgery.
6. *Faraklas I, Yang D, Eggerstedt M, et al. A Multi-Center Review of Care Patterns and Outcomes in Necrotizing Soft Tissue Infections. Surg Infect (Larchmt). 2016*
7. Sartelli M, Guirao X, Hardcastle TC, et al. 2018 WSES/SIS-E consensus conference: recommendations for the management of skin and soft-tissue infections. World J Emerg Surg. 2018;13:58.
8. Phan HH, Cocanour CS. Necrotizing soft tissue infections in the intensive care unit. Crit Care Med. 2010;38(9 Suppl):S460-S468.
9. Hakkarainen TW, Kopari NM, Pham TN, Evans HL. Necrotizing soft tissue infections: review and current concepts in treatment, systems of care, and outcomes. Curr Probl Surg. 2014; Duane TM, Huston JM, Collom M, et al. Surgical Infection Society 2020 Updated Guidelines on the Management of Complicated Skin and Soft Tissue Infections. Surg Infect (Larchmt). 2021
10. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America [published correction appears in Clin Infect Dis. 2015 May 1;60(9):1448. Dosage error in article text]. Clin Infect Dis. 2014
11. Sawyer, Robert G et al. “Trial of short-course antimicrobial therapy for intraabdominal infection.” The New England journal of medicine vol. 372,21 (2015)
12. 10. Lauerman MH, Kolesnik O, Sethuraman K, et al. Less is more? Antibiotic duration and outcomes in Fournier's gangrene. J Trauma Acute Care Surg. 2017
13. 11. Valadez MG, Patel N, Chong V, et al. Short Courses of Antibiotics Are Safe in Necrotizing Soft Tissue Infections. Am Surg. 2021
14. Delaplain PT, Haytham K, Benedict AO, et al. Surgical Infections and the Future of Research: Re-defining the Research Agenda for the Surgical Infection Society. Surg Infect. 2021
15. Tanaka, S., Thy, M., Tashk, P., Ribeiro, L., Lortat-Jacob, B., Hermieu, J. F., Zappella, N., Rozencwajg, S., Snauwaert, A., Atchade, E., Grall, N., Assadi, M., Tran-Dinh, A., & Montravers, P. (2022). Impact of prior antibiotic therapy on severe necrotizing soft-tissue infections in ICU patients: results from a French retrospective and observational study. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology
16. Palma Medina, L. M., Rath, E., Jahagirdar, S., Bruun, T., Madsen, M. B., Strålin, K., Unge, C., Hansen, M. B., Arnell, P., Nekludov, M., Hyldegaard, O., Lourda, M., Santos, V., Saccenti, E.,

Skrede, S., Svensson, M., & Norrby-Teglund, A. (2021). Discriminatory plasma biomarkers predict specific clinical phenotypes of necrotizing soft-tissue infections. The Journal of clinical investigation
17. Garau, J., Blasi, F., Medina, J., McBride, K., Ostermann, H., & REACH study group (2015). Early response to antibiotic treatment in European patients hospitalized with complicated skin and soft tissue infections: analysis of the REACH study. BMC infectious diseases
18. Kao, L. S., Lew, D. F., Arab, S. N., Todd, S. R., Awad, S. S., Carrick, M. M., Corneille, M. G., & Lally, K. P. (2011). Local variations in the epidemiology, microbiology, and outcome of necrotizing soft-tissue infections: a multicenter study. American journal of surgery
19. Khoury, M. K., Heid, C. A., Cripps, M. W., Pickett, M. L., Nagaraj, M. B., Johns, M., Lee, F., & Hennessy, S. A. (2020). Antifungal Therapy in Fungal Necrotizing Soft Tissue Infections. The Journal of surgical research
20. Proud, D., Bruscino Raiola, F., Holden, D., Paul, E., Capstick, R., & Khoo, A. (2014). Are we getting necrotizing soft tissue infections right? A 10-year review. ANZ journal of surgery