Does Negative Pressure Wound Therapy with Instillation Reduce the Bioburden of Infections?

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1) Protocol Title: Does Negative Pressure Wound Therapy with Instillation Reduce the Bioburden of Infections?

2) Purpose of the Study: The purpose of this study is to compare the microbiologic burden and need for further operative debridement of patients undergoing primary surgical debridement of infected tissue, soft tissue abscesses, or traumatic wounds, between patients treated with traditional VAC therapy and those treated with instillation with VAC Veraflo therapy with Cleanse Choice.

Primary endpoint: Bacterial bio-burden as measured by quantitative microbial PCR prior to debridement, immediately following initial debridement, after 2 days of VAC veraflo (or conventional VAC) therapy, and at the time of repeat operative debridements, if needed. We will use the MicroGen PCR platform (DBA Microgen Diagnostics, LLC, Lubbock, TX.) to report on the bacterial burden (reported on a log scale of bacteria per gram) present at the time of debridement.

Exploratory endpoint: Number of operative debridements required prior to reconstruction, number of days until final reconstruction, number of days until decision is made by surgeon that further debridements are no longer necessary, length of hospital stay, wound surface area.

3) Background & Significance:

Plastic, orthopedic, vascular, and general surgeons commonly encounter infections. These may be post-traumatic (e.g. from a laceration while cooking or at the site of a fracture), embolic (seeding of infection from another source), or due to inoculation (e.g. from a contaminated needle used for intravenous illicit drug use). Regardless of the etiology, these patients present with complex problems that often require repeat debridement prior to reconstruction. Their hospital stays are lengthy, painful (in terms of pain from debridement and dressing changes), and expensive (based on the number of repeat operations required to debride infected tissue). The results of the initial surgical debridement are often uncertain- patient and disease factors contribute to the extent and recurrence of the disease and often surgeons will empirically schedule "second looks" to return to the operating room for a repeat debridement/inspection of the wound prior to performing a reconstruction, in order to avoid experiencing a failed reconstruction due to inadequate debridement. A possible cause for failure of reconstruction is the microbial bioburden present in the open wound. We hypothesize that the continuous irrigation as well as the cycles of wound/exudate disruption afforded by the V.A.C Veraflo technology with Cleanse Choice Dressing will reduce the microbial bioburden and possibly the need for operative debridement by allowing for around-the-clock non-excisional debridement and irrigation.

4) Design & Procedures:

Prospective randomized trial. Two arms, 20 patients in each arm. Study team expects to consent/enroll 60 patients in order to achieve 40 subject for evaluation due to voluntary opt-out, inability to return to OR for "second look" debridement on day 2, medical instability preventing further debridement, etc.

Day 0 – (Prior to surgery):

- Consent, randomization, enrollment

Day 1 (day of first operative debridement):

- Patient arrives in the operating room, anesthesia is induced. The extremity is prepared and draped in standard fashion.
- A small piece of tissue (on the order of grams) is excisionally debrided in standard surgical fashion. This tissue **specimen 1** is placed into the plastic specimen collection cup provided by MicroGen, labeled, and the plastic bag containing the cup is sealed. The cardboard box provided in the kit is sealed and, being pre-addressed and pre-paid, is sent to MicroGen in Texas. **The patient receives a random number for use with the MicroGen sample and no identifying information (Name, age, MRN) is sent to MicroGen.**
- Debridement proceeds in standard surgical practice. The prior specimen collection does not rob the lab of tissue that the surgeon, in his/her judgment seeks to send for microbiology culture or pathology.
- At the conclusion of debridement/irrigation, a repeat small piece of tissue **specimen 2** is excised and sent to MicroGen in the same manner.
- At the conclusion of debridement, based on randomization, a wound vac or wound vac with cleanse choice dressing, track pad duo, and saline irrigation is applied. The wound is dressed in standard fashion according to the sugeon's preference (e.g. splint, ACE wrap, etc.).
- Patient emerges from anesthesia, and heads to recovery/floor or ICU as planned.

Day 1 until day 2:

- Negative pressure wound therapy or negative pressure wound therapy with irrigation proceeds automatically, 24/7

Day 2 (second operative debridement):

- Patient arrives in the operating room, anesthesia is induced. The extremity is prepared and draped in standard fashion.
- A small piece of tissue (on the order of grams) is excisionally debrided in standard surgical fashion. This tissue **specimen 3** is placed into the plastic specimen collection cup provided by MicroGen, labeled, and the plastic bag containing the cup is sealed. The cardboard box provided in the kit is sealed and, being pre-addressed and pre-paid, is sent to MicroGen in Texas. **The patient receives a random number for use with the MicroGen sample and no identifying information (Name, age, MRN) is sent to MicroGen.**
- Debridement proceeds in standard surgical practice. The prior specimen collection does not rob the lab of tissue that the surgeon, in his/her judgment seeks to send for microbiology culture or pathology.

- This next step is completely up to the surgeon. Additional debridement, reconstruction, fracture fixation, reconstruction, closure, repeat wound vac. Additional samples are not collected.
- Patient emerges from anesthesia, and heads to recovery/floor or ICU as planned.

Future debridements, if performed:

- Done at Day 5 (+/- 1 day). This is an optional step as many patients will not require additional debridement. Tissue samples will be sent at the time of the third surgery, whether it is a debridement, reconstruction, or other procedure.
- Tissue collection at the start of each further surgery for MicroGenPCR. In the event that wounds are dirty/infected and require repetitive debridements, we may collect as many as n additional samples for n additional operative debridements to track the bioburden over time.

Demographics and data to be collected on participants:

Patient name, age, gender, MRN, height, weight, type of injury, mechanism of injury, concurrent fracture involved with the wound, major vascular injury, prior debridements before presentation, date/time of injury, date/time of ED or hospital presentation, date/time of irrigation in ED (if performed), date/time of preliminary surgery, date/time of additional debridements, reconstructions, number of days until closure/reconstruction, number of days to decision is made that debridement is complete, comorbidities: [diabetes, smoking, steroid use, radiation], lab values: [CBC, BMP, albumin], vital signs. Surgical details: type of anesthesia, surgeon, surgical service, operative time, anesthesia time, type of debridement, level of debridement, whether a concurrent operation was performed, wound area/area of debridement, whether a drain was placed, volume of irrigation, pre-op intra-op and post-op antibiotics. Type of tissue debrided and sent for our samples (and location within the wound). If debridement is abandoned, e.g. if surgeon decides only an amputation will cure this wound.

ICU stay, blood transfusion, mechanical ventilation postoperatively. Date of discharge. Several of these variables, including when the decision is made to reconstruct, may require searching the EMR after discharge. For example, a patient may be sent home with a plan for a nurse to change dressings for weeks at home. The patient may present to clinic after discharge and the surgeon examines the wound then decides to schedule wound closure/reconstruction (e.g. skin graft, flap, etc).
We will follow the patients for the duration of care.

5) Selection of Subjects:

Inclusion criteria:

- Patients age 18 years or older who have an injury or infection for which surgical debridement (in the operating room) followed by VAC application is planned.
- Able to provide informed consent.

- Speak and read English.
- Patients may be immunosuppressed, either through nature of disease or due to medication.
- Patients may be on systemic antibiotics or topical antimicrobials.
- Patients may present with exposed bone or joint space as part of either the debridement or traumatic injury.

Exclusion criteria:

- Patients on therapeutic anticoagulation to treat DVT/PE, atrial fibrillation, etc, for which we would include warfarin, therapeutic heparin or low-molecular-weight heparin, direct oral anticoagulants (e.g. rivaroxaban, dabigatran).
    - Most of these patients are on prophylactic anticoagulation to lower the risk of a DVT (e.g. heparin or enoxaparin subcutaneous injections). We would still like to include those patients in our study. These drugs are given to many hospitalized patients due to their immobility and are not prescribed to the same patients once they are safely living at home again. Additionally, many patients are on aspirin for the coronary prevention factor and we do not even usually hold this prior to surgery (even if someone wanted to, it takes days of waiting to reverse the platelet effects and these are acute wounds/infections). We would also like to include patients on aspirin or clopidogrel (anti-platelet agents), for example.

6) Subject Recruitment and Compensation: A maximum of **60** subjects will be consented in order to achieve 40 evaluable subjects. Duke subjects will be introduced by their healthcare team and if interested in participating, will be given more information by the research team. Potential subjects will be screened in the ED or Hospital and identified by an investigator or a member of the research team. An investigator will confirm eligibility criteria and a member of the site study team will notify the sponsor of a potential candidate for the study after the subject has been consented.

There is no subject compensation planned for this study.

7) Consent Process: Subjects will be introduced to the study by their physician and then the study team will provide additional information and consent if subjects are interested in participating in the study. See iRIS consent section for additional consent details.

Patients will be approached after permission is granted by a member of the care team.

These infections or injuries may present at "inopportune times", e.g. early hours of the morning and be posted for surgery to commence in the next several hours to days. If a patient is interested in participation, they will have the opportunity to discuss research up to the time they are entered into pre-op holding.

8) Subject's Capacity to Give Legally Effective Consent: Only subjects able to give legally effective consent will be permitted to participate in this study.

9) Study Interventions: Instillation within the wound vac

From the manufacturer (Veraflo with cleanse choice):

> The unique three-layer design of the V.A.C. VERAFLO CLEANSE CHOICE™ Dressing promotes a wound cleansing option that facilitates removal of thick exudate material, such as fibrin, slough and thick wet exudate, and other infectious material, to provide a wound cleansing option for clinicians when surgical debridement must be delayed or is not possible or appropriate.

From the manufacturer (Conventional VAC):

> When used on open wounds, they are intended to create an environment that promotes wound healing by secondary or tertiary (delayed primary) intention by preparing the wound bed for closure, reducing edema, promoting granulation tissue formation and perfusion and by removing exudate and infectious material. Open wound types include: chronic, acute, traumatic, subacute and dehisced wounds, partial-thickness burns, ulcers (such as diabetic, pressure or venous insufficiency), flaps and grafts.

10) Risk/Benefit Assessment: We do not yet know if the instillation affects the time to healing or the number of debridements required. Both the wound vac and vac with instillation are standard-of-care interventions, not currently known to present any additional risk to subjects. The variable that most directly affects the patient is the length of wound therapy and/or number of operative debridements required.

11) Costs to the Subject: There will be no additional costs to subjects for participating in this study. The two methods are both standard of care. The study drug/device will be provided at the standard cost to the patient. These are patients who were already selected to be managed with negative pressure (wound vac) wound therapy, the difference will be the type of vac dressing that they receive.

12) Data Analysis & Statistical Considerations:

Primary endpoint: Bacterial bio-burden as measured by quantitative microbial PCR prior to debridement, immediately following initial debridement, after 2 days of VAC veraflo (or conventional VAC) therapy, and at the time of repeat operative debridements, if needed. We will use the MicroGen PCR platform (DBA Microgen Diagnostics, LLC, Lubbock, TX.) to report on the bacterial burden (reported on a log scale of bacteria per gram) present at the time of debridement.

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Dr. Blau to do analysis using JMP (SAS) software. Will use t-test for log scale of bacteria per gram.

Power analysis for a one-way ANOVA with 2 groups was conducted to determine a sufficient sample size using an alpha of 0.05, a power of 0.80, and a large effect size (f = 0.40) Based on the aforementioned assumptions, the desired sample size is 25.52. Original funding called for 60 patients, but funding agency subsequently retracted their offer to cover indirect costs, so the sample size was decreased to 40 patients total as the grant now must absorb the indirect costs.

13) Data & Safety Monitoring:

All adverse events related to the study will be signed off on by the PI and reported to the IRB in accordance with Duke and HIPAA policies.

14) Privacy, Data Storage & Confidentiality: Any data that is stored in paper or non-digital format will be locked in a file cabinet within a controlled access office. The office will be locked when not in use by the study team. All electronic study information will be stored on the secure Surgery Server in the IRB folder for this study with access limited only to the study team. All study information will be stored in accordance with the RDSP for this study.

Confidentiality of subject data will be ensured by de-identification of subject data. During data collection, subject identifiers and relevant data elements will be recorded in the database. Then, study-specific identification numbers will be assigned to each subject. Prior to dissemination of any information in this database beyond the DUMC's secure servers or firewall, all identifiers will be stripped from the database and data will only be referenced by the study-specific identification numbers.

The adequacy of the Research Data Security Plan will be evaluated and approved by the Surgery CRU and IT personnel prior to study conduct.

Any publications or presentations that result from this research will not identify any subjects individually, and will present data in aggregate form only.