Study Title: A PILOT STUDY TO EVALUATE THE EFFICACY OF VACUUM-ASSISTED DRESSINGS (V-AD) IN THE MANAGEMENT OF OPEN CHEST WOUNDS

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A. GENERAL STUDY INFORMATION

A.1. Study Title: A PILOT STUDY TO EVALUATE THE EFFICACY OF VACUUM-ASSISTED DRESSINGS (V-AD) IN THE MANAGEMENT OF OPEN CHEST WOUNDS

A.2. Investigators

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B. STUDY PURPOSE

B.1. Hypothesis: Vacuum-assisted dressings (V-AD) are effective in treating patients with open chest wounds (OCW) and will decrease the time-to-closure of such wounds when compared to a historical cohort of patients managed by traditional wound care management.

B.2. Aims:

a. Obtain definitive evidence for the effectiveness of V-AD in the management of OCW through a well-designed prospective pilot study conducted at 2 campuses of Mayo Clinic (Florida and Rochester).
b. Compare the rate of healing (time-to closure) of OCW in patients treated with V-AD to a historical cohort of patients with OCW treated at Mayo Clinic without V-AD. Time to wound closure further being defined as the total approximation of the wound edges to close the defect.
c. Determine if treatment with V-AD reduces the need for additional procedures to close wounds, such as muscle flaps.

C. BACKGROUND

Pleural space infections (empyemas) can occur either spontaneously or in the postoperative setting after any type of thoracic or abdominal surgery. The management of infected thoracic cavities has been one of the most frustrating problems encountered by thoracic surgeons. Post-operative infections occurring in the presence of concomitant bronchopleural fistulas (BPF) increase the complexity of treatment even more. While in many cases of empyema temporary drainage and antibiotic therapy will help resolve the infection, in others a more permanent drainage method such as an open chest window (a.k.a Eloesser window) may be required. The resulting open chest wounds

require frequent debridement and daily dressing changes for unspecified duration, imposing a tremendous financial and mental burden on the caretakers and patients. In addition, access into the chest cavity during dressing changes can be difficult and painful, which can result in small pockets of undrained infection.

Due to chronic infection and the large space that exists, these wounds may take months or even years to close by secondary intention. In order to expedite the closure of the wound, additional procedures such as modified Clagett procedure (advancement of muscle flap) or thoracoplasty (collapse therapy) are often performed once the infection subsides. These operations can be quite morbid and are not always successful in obliterating the space in the chest cavity.

The technical and psychosocial challenges encountered in managing these chronic wounds have led to the more recent use of V-AD as an alternative way of management (1-15). V-AD has a well-established role in the management of chronic, large wounds in skin and other soft tissues including the sternum and abdomen, and has been approved by the FDA for this purpose (FDA #). The negative pressure not only helps in effective drainage but also promotes growth of granulation tissue, leading to faster closure of wounds. However, the actual role of V-AD in the management of open chest wounds has not been evaluated in a well-designed prospective trial. To the best of our knowledge, there are currently no data that compares V-AD to traditional open chest wound management techniques. One prospective trial using the mini-VAC with instillation therapy in patients without BPF reported success in 86% of patients (5). Small retrospective cases series and individual case reports have reported varying results with some success noted (1,2,4,6). Reported advantages of using V-AD include decreased frequency of dressing changes and a decrease in the time needed to heal. Pain with application of the V-AD and difficulty in removing the dressings due to impaction have been described as some of the disadvantages (5). A best-evidence review of 23 publications on this topic suggested that V-AD might have some benefits as an adjunct to standard treatments but recommended clinical trials to understand this better (7).

D. SUBJECT INFORMATION

D.1. Target accrual

A total of 10 patients will be enrolled in the intervention (V-AD) arm of the study. These patients will be recruited from those presenting to Mayo Clinic Florida or Mayo Clinic Rochester with thoracic infections that require surgical intervention. A historic control group of 10 patients with open chest wounds who were treated with the traditional treatment techniques at Mayo Clinic will be selected using propensity-matching methods. We plan to complete our target accrual over a timeframe of approximately 12 months.

D.2. Subject Population

Subjects will be identified by the Principal Investigator or the Co-Investigators. Patients referred for surgical management of thoracic infections, who meet inclusion criteria and none of the exclusion criteria, will be invited to participate in the study. If the subject is interested in more information about

the study, a study coordinator will meet with the patient to discuss further and obtain informed consent.

D.3. Inclusion criteria

1. Subject provides informed consent and is:
    a. ≥18 years of age,
2. Subject is scheduled to undergo surgical intervention(s) as part of the standard care for management of intrathoracic infection.

D.4. Exclusion criteria:

D.4.1. Patients who have the following conditions will be excluded from participating:

1. Patent bronchopleural fistulas.
2. Severe respiratory failure requiring mechanical ventilation at the time of first consultation.
3. Inability to provide informed consent due to physical or mental impairment.
4. Altered mental status.
5. Proven or suspected malignancy in the wound.
6. Coagulopathy due to medical or pharmacologic reasons.
7. Dependency on anticoagulants or antiplatelet medication due to high risk for adverse events if these medications are stopped for a prolonged period of time.
8. Allergy to acrylic products.
9. Subject is a pregnanat or lactating female

D.4.2. Patients in whom the use of V-AD is determined to be unsafe by the surgeon for any reason will be excluded from the study.

D.5. INITIAL EVALUATION AND INFORMED CONSENT FOR ENROLLMENT

All patients presenting with an infection in the pleural cavity that requires surgical intervention (exploration, debridement, washout, decortication, etc.), and meet inclusion criteria will be informed about the study by the surgeon prior to the operation. If the initial meeting occurs during regular working hours (8am to 5pm), the study coordinator will review the consent form with the patient and answer any questions that the patient may have about the study. The patient will be reminded that their participation is voluntary, they can withdraw at any time and their care at Mayo Clinic will not be affected whether they choose to participate or not. If the initial consultation is done after regular working hours or on an emergency basis, the surgeon will discuss the availability of the study but will wait till the study coordinator is present to obtain formal consent. In such instances where the patient subsequently consents to being enrolled in the study, the V-AD will not be applied until the next dressing change.

Due to the patient's surgery procedure and other factors patients will be continually assessed for loss or gain or capacity to consent. If it is determined to obtain assent from a patient this will be documented in the patient's medical record. If the patient re-gains capacity to consent, then the patient's consent will at that time be obtained.

E. STUDY DESIGN

E.1. **Methods:** This will be a prospective pilot study of 10 patients with OCW treated using V-AD at Mayo Clinic in Florida and Rochester.

E.1.2. **Procedure for placement of V-AD and subsequent monitoring, including dressing changes.**

E.1.2.1. Initial assessment and V-AD application:

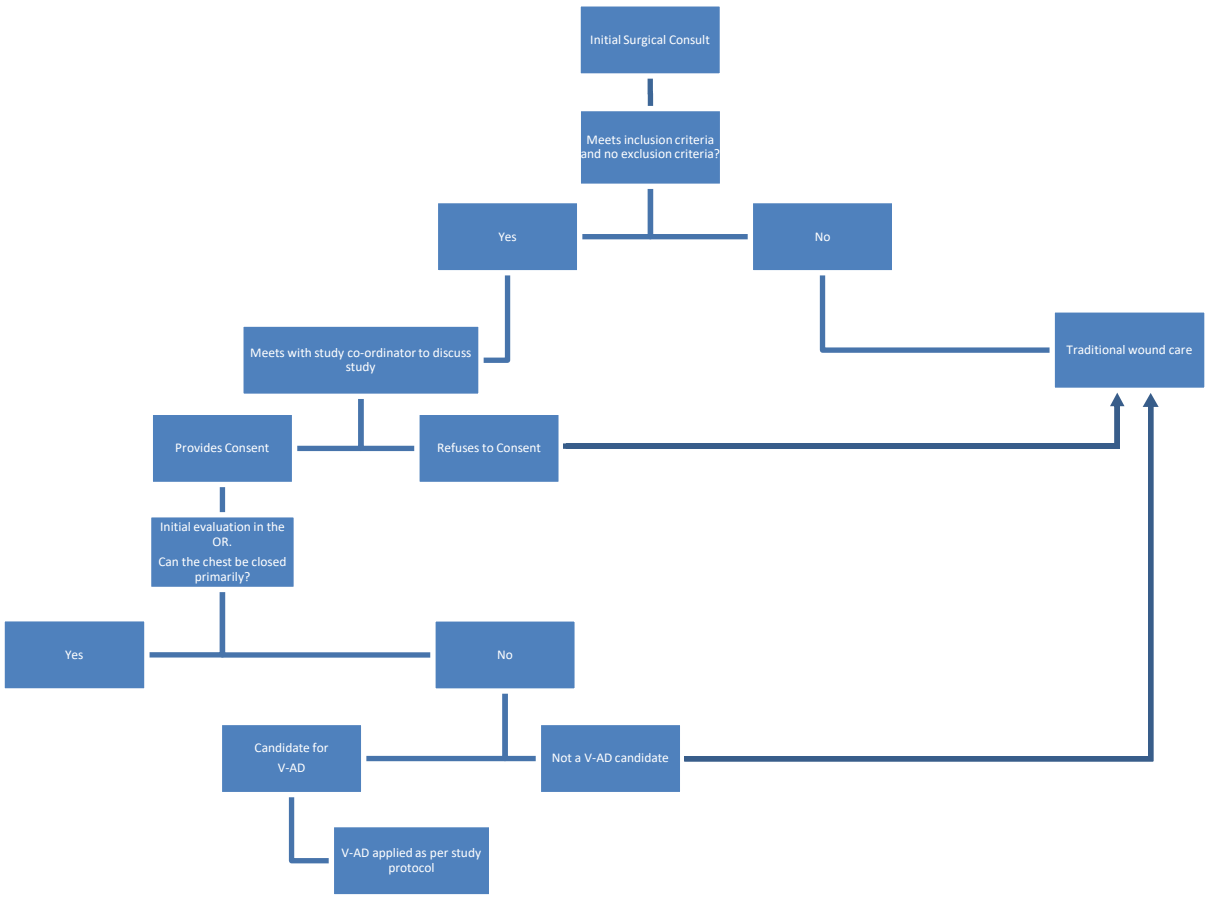
After obtaining informed consent from eligible patients, they will be taken to the operating room for the initial assessment and treatment as determined by the surgeon. The intervention may include, but is not limited to, thoracotomy, minimally invasive thoracic surgery, washout, excisional debridement, pulmonary decortication, pulmonary resection and closure of any obvious bronchopleural fistulas. Aerobic and anaerobic tissue cultures from the infected space will be obtained at the time of surgery. The surgeon will determine if the chest can be closed primarily. If unable to do so due to obvious infection or perceived high risk of developing a subsequent deep space abscess, the surgeon will next assess whether the wound is suitable for management with V-AD (V.A.C.® Therapy, KCI, San Antonio, TX). In the absence of any contraindications, the OCW will then be packed with one or more foam sponges and an airtight transparent dressing. At the time of application, these sponge dressings can be cut to fit within the wound. The type of dressing (black or white foam) to be used will be determined by the surgeon depending on the characteristics of the wound bed. The dressing will then be connected to the negative pressure canister unit and maintained on continuous negative pressure ranging from -75 mmHg to -125 mmHg. Unless otherwise indicated, the dressing will be changed once every 72 hours under IV sedation or anesthesia.

The patient will be admitted to the hospital for at least two supervised dressing changes, at which time the surgeon will re-assess the wound to determine if it can be closed with or without a soft tissue (muscle, omentum, etc.) flap. Wounds determined to be not ready for closure will then be repacked with the V-AD. If no other indication for inpatient hospital care exists other than the V-AD, the patient will be then discharged home or to a skilled nursing facility where the remainder of dressing changes will be performed. If the patient cannot be safely discharged from the hospital, inpatient care will be continued.

After discharge, the patient will return to the outpatient clinic for wound inspection and dressing change by the surgeon once every two weeks and earlier, if necessary. During hospitalization and clinic visits, a Mayo Clinic photographer or a provider authorized to use the Mayo Clinic imaging software will photograph the wound, which will be a part of the permanent medical record of the patient. At every

dressing change in and outside the hospital, the number of individual pieces of foam sponges will be entered in a logbook and accounted for during removal at the next change.

Figure 1: Algorithm for Patient Selection and Enrollment



E.1.2.2. Monitoring:

A prospective database of all patients in the study will be maintained and will record the following:

a. Name, Medical Record number and Dates of dressing changes
b. Pain scores – visual analogue scores,
c. Ease of dressing changes (Easy, moderately difficult, very difficult)
d. Wound bed characteristics including amount of granulation tissue (minimal, moderate and significant) and dimensions (length x breadth x depth in centimeters).
e. Duration of treatment
f. Adverse events

E.1.2.3. Discontinuation of V-AD therapy:

1. In the absence of a noticeable improvement in the wound bed after 2 weeks of continuous V-AD therapy, the treatment plan will be re-assessed and the determination will be made as to whether the V-AD therapy should be discontinued.

2. The V-AD will be discontinued if the patient develops severe uncontrolled pain that does not respond to pain medications or a reduction in the negative pressure to -50 mm Hg.

3. In the event of any unpredicted adverse event, such as bleeding, injury to underlying organs, new onset of respiratory distress or allergy to the dressings will result in removing the V-AD.

4. Patients who require treatment with anticoagulation or antiplatelet agents after V-AD application will be removed from the study to avoid hemorrhagic complications.

F. DRUGS/ SUBSTANCES/ DEVICES

The V.A.C. Therapy System has many components that work together to apply negative pressure to wounds. The components include:

1. a porous foam dressing which comes in contact with the wound base and equally distributes negative pressure throughout the wound,
2. an airtight transparent adhesive drape that covers the foam dressing and
3. a software-controlled V.A.C Canister that is connected to the dressing by means of a transparent plastic tubing.

There are 2 types of foam dressings that will be used in the study:

1. An open pore reticulated polyurethane foam (V.A.C Granufoam Dressing)
2. A polyvinyl alcohol foam (V.A.C WhiteFoam Dressing).

The canister system is self-monitoring and can be set to different therapy modes (continuous or intermittent) depending on the individual patient and wound needs. In-built alarm systems can detect a loss of pressure or tubing blockage, alerting the care team to troubleshoot these issues.

G. DATA ANALYSIS

Exploratory analysis will be used to analyze the correlative studies comparing the healing rates. The analysis will include all 10 patients treated with V-AD and a matched group of 10 patients previously treated for empyema at Mayo Clinic. Due to the limited sample size the analysis will be descriptive and hypothesis generating. Any information that shows promise based on the pilot data will be explored in follow-up studies. Descriptive statistics, and scatter plots with 95% confidence intervals will graphed over time. Data will be visually inspected for differences.

The following datasets will be compared during analysis:

1. V-AD treated patients versus historical controls.

H. RISKS

H.1. <u>Potential risks:</u> The specific risks of V-AD use in the chest cavity have been reported and include pain, hypotension and difficulty in removing the sponge (11). No serious adverse events have been reported to date. General risks of NPWT when applied to other parts of the body include suction injury to skin and injury to underlying organs such as bowel or blood vessels. Extrapolating these adverse effects to the chest, there is an unquantifiable risk of injury to intrathoracic organs – lungs, heart, large vessels (aorta, pulmonary artery or veins). Hypothetically, injury to the lungs can lead to worsening of bronchopleural fistulas, air leaks or pulmonary hemorrhage; injury to the vascular structures can lead to significant hemorrhage, and even death. During removal of the black foam sponge dressing, it is possible to cause injury to the underlying structures due to excessive traction or adherence from tissue ingrowth.

H 1.1. Potential Severe Adverse Events

- Death
- Respiratory failure requiring ventilation (for any cause)
- Major cardiac arrhythmias requiring cardioversion or hospitalization which are hemodynamically significant.
- Massive Hemoptysis (life-threatening or requiring an intervention e.g. embolization)
- Intra-parenchymal/intrapleural hemorrhage leading to hemodynamic instability or requiring any intervention to specifically address the bleeding.
- All new onset bronchopleural fistulas will be reported as SAE's.
- Worsening of pleural space infection requiring treatment with IV antibiotics, with exceptions as below:
    - <u>Treatment of pathogens identified on microbiology obtained during the initial culture will not count as a new infection.</u>
    - Requirement for sharp debridement of necrotic tissue or exudates identified during dressing changes will not be considered an adverse event, as this is normal during management of infected wounds.

H.1.2. Other Adverse Events

- Minor cardiac arrhythmias NOT requiring cardioversion, hospitalization and/or are NOT hemodynamically significant.
- Minor Hemoptysis or minor intra-parenchymal/intrapleural hemorrhage
- Pneumonia/pleural space infection treated as outpatient
- Mild (<u>≤</u>4/10, not requiring IV medication) to moderate pain (requiring IV medication or rated as >5/10)
- DVT or Pulmonary Embolus treated with anticoagulation alone

H.2. Risk Prevention and Monitoring: In order to decrease the risks of these potential adverse events, the following safety precautions will be taken:

1. The dressings will not be applied directly in contact over any exposed blood vessels, heart or lung, or anastomotic sites.
2. Mepitel® (Mōlnlycke Health Care, Norcross, GA), a silicone-based perforated non-adherent dressing will be placed over any delicate organs such as the heart or the lung. This will prevent adherence of the foam dressing to the underlying tissue while allowing drainage. Mepitel® itself can be easily removed as it is non-adherent.
3. The black foam dressing will not be used directly over any organ/structure likely to be traumatized during removal of the dressing. Instead, the white foam will be used as the first layer. The black foam may be placed over the white foam in such instances.
4. Prior to removal, the dressings will be thoroughly soaked with normal (0.9%) saline to disengage the dressings easily.
5. The number of individual pieces of foam dressing placed during each dressing change will be documented and care will be taken to ensure that the same number of dressings is removed (and documented). In case there is a discrepancy in the tally of foam pieces placed and removed in consecutive dressing changes, the surgeon will be contacted immediately. V-AD will not be reapplied until the surgeon confirms that no foam piece has been retained in the wound by personally examining the wound.

We plan to monitor and report all of the above adverse events from the first application of the V-AD to one week after final closure of the wound or termination of V-AD therapy. All standard precautions will be taken to minimize risk. Patients will be monitored in a telemetry unit during hospital admission for complications including bleeding, hemodynamic instability (heart rate < 60 or > 120, systolic BP <90 or > 150, diastolic BP < 50 or > 100, respiratory compromise (SpO2 < 92% on room air).

All data regarding risk/adverse events will be collected in person while the patient is admitted to the hospital or seen in clinic or over the telephone if the patient is outpatient.

The primary endpoint of this study is efficacy of treatment. However, safety is also a critical component and will be defined by the rate of severe adverse events (see below). In addition to major complications, all intermediate and minor complications will also be recorded.

H.3. Evaluation and Grading of Adverse Events

H.3.1. Performing Adverse Events Assessments

The Principal Investigator will be responsible for promptly documenting and reporting all adverse events (AEs) observed during the study. If the AE is considered severe, the investigator must report the AE immediately to the DSMB through Mayo Clinic Rochester. All AEs considered "severe" will be reported no later than 24 hours after the investigator recognizes/classifies the event as a severe adverse event.

For all SAE's, the study will be placed on hold until the DSMB has reviewed and notification received to continue study accrual. The safety monitoring board may require study protocol modifications or cessation of all study activities prematurely.

H.3.2. Adverse Event Definitions

The following definitions of terms are guided by the International Conference on Harmonization, the U.S. Code of Federal Regulations [21 CFR 312.32] and European Union Directive 2001/83/EC and are included herein. An adverse event will be defined as any unexpected medical event associated with the use of the procedure in a human subject, whether or not considered directly procedure-related. An adverse event can be any unexpected or abnormal clinical sign or condition temporally associated with the procedure.

H.3.3. Severity of Adverse Events

Adverse events are graded based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

H.3.4. Communicating Severe Adverse Events

The principal investigator accepts all responsibilities for AE identification, documentation, grading, and prompt notification of the safety monitoring board no later than 24 hours after the occurrence of the event. The board will then have 24 hours to review the provided data, determine the appropriate course of action including possible modification of the existing protocol, temporary study hold or study cessation.

I. BENEFITS

There is no guarantee that the subjects will receive any benefit from this study. The research team hopes that the use of V-AD will lead to faster closure of the open chest wound by eliminating infection and promoting granulation tissue, but this remains hypothetical.

J. PAYMENT AND REMUNERATION

Subjects will not be paid to participate in the study.

K. COSTS

There will be no additional costs to subjects for participating in this study. Subjects and/or their insurance companies will be responsible for all care provided as part of the wound care with V-AD as this service is part of the standard of care they would receive for their condition.

Any costs related to laboratory analysis that is not considered standard of care, will be covered by the investigator group.

L. RESOURCES

TSFRE grant $25,000

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