Protocol Title: Octreotide for Management of Bronchorrhea in Mechanically Ventilated Patients: A Randomized Controlled Trial.

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Background:

It is well known that the ability to support the critically ill has greatly been impacted since the arrival of mechanical ventilation (MV). MV is considered an essential tool used in the Intensive Care Units (ICU) in today's world with up to 38% of patients in the ICU requiring MV [1].

One of the main challenges faced by ICU providers caring for mechanically-ventilated patients is management of airway secretions, which is essential for decreasing the risk of serious complications, including ventilator-associated pneumonia, a serious problem with an estimated incidence of 4 to 40 percent and an all-cause mortality of 20 to 60 percent [2,3]. Copious airway secretions may also be a major barrier to extubation, which would prolong time on mechanical ventilation and further increase risk of ventilator-associated pneumonia and other serious complications.

Patients suffering from conditions associated with overproduction of mucus and impairment of its clearance, such as asthma, chronic obstructive pulmonary disease, and history of smoking, often require mechanical ventilation. Although mechanical ventilation is often lifesaving, controlling airway secretions in these patients is especially challenging.

Over the years, numerous studies have looked at various interventions that can help to manage secretions and improve outcomes [4,5,6,7]. As a result, a number of non-pharmacologic interventions, mucolytics, and mucoregulators have become the standard of care for mechanically-ventilated patients. Mucolytics, such as Mucomyst and Mesna, alter viscoelastic properties of mucus to improve its clearance. Aerosolized anticholinergics, glucocorticoids, and β2-adrenergic agonists are the currently used mucoregulators, which decrease mucous production and secretion[15]. However, some patients demonstrate excessive airway secretions, also known as bronchorrhea, that persist despite these interventions.

Unfortunately, no standard recommendations exist to guide clinicians in management of bronchorrhea resistant to standard interventions. Systemic glucocorticoids (in addition to aerosolized ones), macrolide antibiotics, and scopolamine patch (a systemic anticholinergic) have been routinely used by intensivists in such situations. Remarkably, little data exist on the use of systemic glucocorticoids and macrolides in ventilated patients, and most of the knowledge is provided by clinical trials assessing long-term effects of such agents in patients with underlying chronic respiratory diseases[15]. Most data on effectiveness of scopolamine is limited to case reports describing its use in palliative care.

Octreotide is another agent with mucoregulatory properties. It is a synthetic analogue of a hormone somatostatin and functions as an anti-secretory drug by inhibiting synthesis of pituitary and gastrointestinal hormones. One of the hormones inhibited by octreotide is secretin - a potent stimulant of electrolyte and water movement in the gastrointestinal system. As lungs have secretin receptors too, it has been suggested that inhibiting secretin also reduces chloride and water efflux from bronchial epithelial cells, thereby reducing sputum production [8,9,10]. In fact, several case reports have emerged about its effectiveness in cancer patients with bronchorrhea [8, 11, 12]. Remarkably, these case reports demonstrated its effectiveness in patients who failed to respond not only to the standard treatments but also to systemic glucocorticoids and scopolamine. For instance, Hudson et al. described the successful use of octreotide (300-500 mcg/24 hrs) through subcutaneous route to manage the symptoms of bronchorrhea in a 74-

year-old female with bronchioloalveolar cell carcinoma [8]. The patient was producing more than 1 L of sputum per day and after two days of octreotide therapy, sputum production subsided completely. Pahuja et al. reported similar results with octreotide administered as intravenous infusion, in a 47-year-old female with bronchioloalveolar cell carcinoma [11].

As described above, scopolamine is one of the interventions routinely used by intensivists to manage excessive bronchial secretions in patients who have failed the standard measures. Similarly to octreotide, it inhibits both bronchial and gastrointestinal secretions. Remarkably, in a recent randomized control, octreotide was shown to be superior to scopolamine for symptom control in patients with increased gastrointestinal secretions due to bowel obstruction [13,14].

Given the fact that no quality evidence-based information is available to guide ICU clinicians in management of bronchorrhea that has failed to respond to standard interventions, as well as the promising results described in case reports, we propose a randomized controlled trial that would compare effectiveness of octreotide to other interventions that have been used to control bronchial secretions in mechanically-ventilated patients.

Octreotide is widely available and has a relatively low cost (about $17/day in our hospital). In the United States, it has been used widely in outpatient and inpatient settings for over 16 years, mostly for various endocrinopathies and gastrointestinal variceal bleeds but also for a number of other pathologies. It is considered by clinicians to be an overall well-tolerated medication, with fewer significant side-effects compared to systemic steroids and scopolamine. If octreotide is proven to be an effective mucoregulator, it may become an essential tool used in the intensive care units throughout the world.

Objectives/Purpose of the study:
The purpose of this study is to evaluate effectiveness of including parenteral octreotide (12-25 mcg/hour for 72 hours) in addition to the other standard of care treatments deemed necessary by the ICU attending physician in managing bronchorrhea in mechanically ventilated patients. It is hypothesized that octreotide decreases excessive bronchial secretions and shortens time to extubation.

Trial Design:
This study is an open-label, randomized controlled trial. Patients will be randomized into two groups of 15, "Routine Care" group, which will serve as the control group, and "Octreotide" group. The amount of bronchial secretions is routinely measured in all mechanically ventilated patients. Once the Primary Team identifies a patient as a candidate for the study, the study team will review their medical records and assess the patient based on the inclusion and exclusion criteria to determine if they are qualified to participate in the study (screening). If the patient is qualified, one of the study members will explain the research project to the patient or his/her authorized representative and also explain the informed consent process. This study does not compensate patients for participating in the study or for any potential injuries/illness arising out of their participation in this study. This aspect will be made clear to the patients (or their authorized representative) in addition to other risks and benefits of participation in this study. If the patient or his/her authorized representative agrees to participate in the study informed consent will be obtained. After informed consent, the patient will be administered

standard of care medications for the first 24 hours after the screening and a baseline volume of bronchial secretions during this 24 hour period will be recorded. Additionally, medications administered and procedures performed during this 24 hour period would also be recorded. Then, a security envelope containing group assignment will be opened by the ICU attending physician. Both groups will continue to receive treatments that have already been initiated to manage bronchial secretions. In addition, "Octreotide" group will receive parenteral octreotide, while "Routine Care" group will not receive any additional treatment for the study. All patients will continue to receive the care deemed necessary by the ICU attending physician and his/her team. These interventions will be continued for 72 hours or until extubation or withdrawal from the study, whichever occurs earlier. Subsequently, the standard of care management, as determined by the Primary Team, will be continued.

Medications and procedures performed as part of the standard of care while the patient is on octeroide (for the "Octerotide" group) and 24 hours after admission (for the "Routine Care" group) will be recorded for the next 72 hours or until extubation or withdrawal from the study, whichever occurs earlier. Additionally, for patients in the "Octerotide" group, the rate, dose and mode of octerotide administration will be recorded on an octerotide administration log. The rate of bronchial secretions will be measured and recorded twice daily; the changes, relative to the baseline measurements, will be compared between the groups.

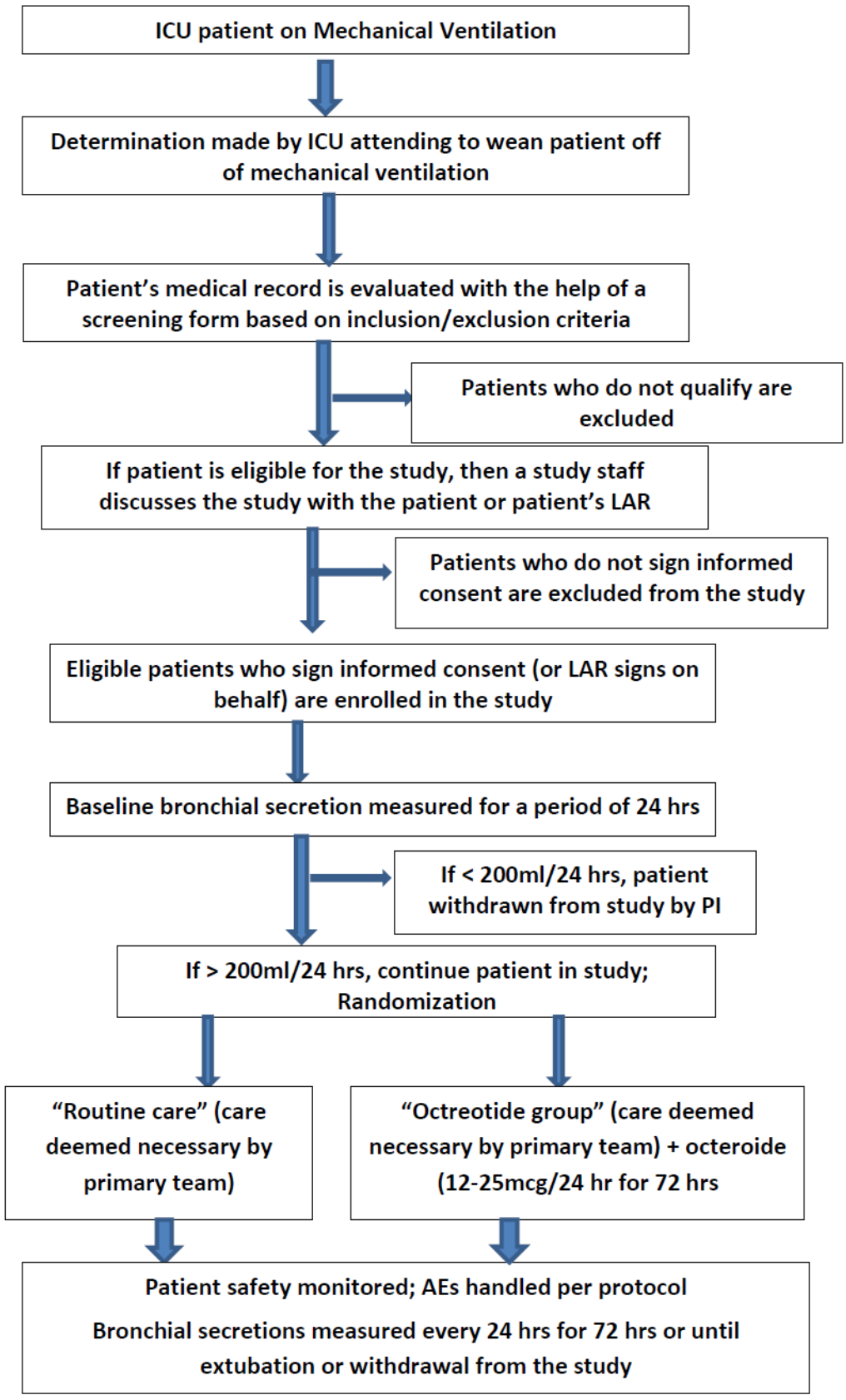
ICU patient on Mechanical Ventilation
Determination made by ICU attending to wean patient off of mechanical ventilation
Patient's medical record is evaluated with the help of a screening form based on inclusion/exclusion criteria
Patients who do not qualify are excluded
If patient is eligible for the study, then a study staff discusses the study with the patient or patient's LAR
Patients who do not sign informed consent are excluded from the study
Eligible patients who sign informed consent (or LAR signs on behalf) are enrolled in the study
Baseline bronchial secretion measured for a period of 24 hrs
If < 200ml/24 hrs, patient withdrawn from study by PI
If > 200ml/24 hrs, continue patient in study; Randomization
"Routine care" (care deemed necessary by primary team)
"Octreotide group" (care deemed necessary by primary team) + octeroide (12-25mcg/24 hr for 72 hrs
Patient safety monitored; AEs handled per protocol
Bronchial secretions measured every 24 hrs for 72 hrs or until extubation or withdrawal from the study

Figure 1. Trial design.

Electronic medical records of the subjects will be retrospectively reviewed to collect the following data recorded by the Primary Team during the ICU stay: demographic information, past medical history, smoking history, diagnoses and problem list, vital signs, diagnostic test data, medications, and procedures performed during the entire length of stay during which the subjects participated in the study.

If a patient has decision-making capacity, an informed consent will be obtained from the patient. Otherwise, an informed consent will be obtained from the person who has a legal authority to make healthcare decisions for the patient.
To minimize bias, patients will be randomized into the two groups of 15 using a random list generator (http://www.random.org/lists/). The research coordinator will be responsible for maintaining randomization and will place treatment assignments into security envelopes, which will be stored in the ICU intensivist workroom with code-protected entrance.

Each participant's involvement in the study is expected to last approximately 72 hours, plus the time that is necessary to ensure accurate measurement of baseline secretions rate (for up to 24 hours).
While enrolled in the study, management of medical problems other than increased bronchial secretions will not be affected by participation in the trial, and the subjects will receive all the interventions that are recommended by the Primary Team. Management of bronchial secretions, using non-pharmacologic and pharmacologic interventions, is an essential element of care for all mechanically-ventilated patients. This includes anticholinergics, glucocorticoids, and β2-adrenergic agonists that can be used, if indicated, to regulate mucus production; they are usually administered in aerosolized form according to a respiratory-therapy driven protocol. However, some patients experience excessive bronchial secretions (bronchorrhea) despite these interventions. Currently, there are no evidence-based guidelines and no institutional protocol to guide clinicians in such situations. The standard of care to manage excessive bronchial secretions may vary among patients. For "Routine care", some physicians may continue previously started interventions such as inhaled medications (beta-agonists, anticholinergics, and corticosteroids), while others may also use systemic steroids, systemic anticholinergics, or macrolide antibiotics. It has to be noted that some of these standard of care treatment options may also not have a strong research validation to support their use[15].

It is possible that the members of the primary team and the study team overlap, meaning that the ICU attending physician and residents who are part of the primary team for a given study subject may as well be the PI or the co-investigators in this study. The following are the study related responsibilities of the study team staff, irrespective of whether they are part of the primary team or not.

1. After initial alert from the Primary team, review patient medical record for exclusion/inclusion criteria, discuss the study including the fact there is no compensation for illness/injury related to the study to the patient or authorized representative and if the patient (or representative) agrees to participate, obtain informed consent and enroll the in the study.
2. Assign and monitor randomization

3. Obtain baseline sputum collection.
4. Assess the dosage of octeroide infusion within the range prescribed in this study, document and monitor the administration.
5. Monitor subjects for the development of any adverse events including continuous and monitoring of their heart rate, other vital signs every hour and blood glucose level every 4 hours and take remedial measures as approved by this protocol including withdrawing the administration of octeroide.
6. Document the monitoring of vital signs and blood glucose levels (every 4 hrs) in a separate safety monitoring log for the study.
7. Monitoring sputum collection every 24 hrs by the primary care team and document the sputum volumes in the data collection tool.
8. Documenting medications and procedures used by the primary care team for the routine care group (control) during the 72 hour period post-baseline.

Potential Risks and Benefits

Subjects in the "Routine Care" group will ONLY receive treatments deemed necessary by the Primary Team. Macrolide antibiotics, systemic anticholinergics, such as scopolamine patch and glycopyrrolate, and systemic steroids are commonly used remedies for excessive bronchial secretions that have not responded to standard interventions such as inhaled beta-agonists, anticholinergics, and corticosteroids . These medications have a variety of potential side effects, including severe and lethal ones. However, the risk for subjects enrolled in the "Routine Care" arm will be no different from patients not participating in this study, as the subjects will receive interventions deemed necessary by the Primary Team, similarly to the patients not participating in the study.

Subjects in the "Octreotide" group will receive parenteral octreotide (dosage range 12-25mcg/hour) for 72 hours in addition to the treatments deemed necessary by the Primary Team. The list of potential side effects can be found in the Addendum #1. Octreotide has been widely used in the treatment of other conditions and diseases and is considered to be well-tolerated. Its overall side effect profile is favorable compared to systemic steroids and anticholinergics. These risks will be minimized by a short duration of use (72 hours); the doses used in this study are significantly below the maximum recommended dose (1,500 mcg/day) for other indications (see Appendix 1). The subjects will be closely monitored for any signs of adverse events, and the dose of the medication will be reduced, or its administration will be stopped, if a subject develops a clinically significant adverse reaction.

Also, subjects in both groups will be at risk that their bronchial secretions are not well controlled. However, it is expected that at the time of enrollment, the subjects will already be receiving nebulizer treatments, which is the standard of care for management of mechanically ventilated patients; the study will compare additional interventions for which no quality evidence-based data exists so far.

Subjects may benefit from this study by experiencing better control of their bronchial secretions, which may shorten duration of mechanical ventilation and decrease risk for related complications. The information learned from this study may help other patients requiring mechanical ventilation.

Selection and Withdrawal of Subjects:
Inclusion criteria:

- Patients are being weaned from mechanical ventilation
- Excessive bronchial secretions (over 200 ml/24 hours) is deemed by the Primary Team to be a major barrier to extubation

Exclusion criteria:

- Known hypersensitivity to octreotide
- Persistent bradycardia (HR < 60)
- Mobitz type II or 3rd degree heart block in patients without a pacemaker
- Active septic shock
- Patients being treated with intravenous agents for hypertensive urgency or emergency
- Cardiac surgery patients
- Initiation of therapy with systemic or inhaled steroids within 72 hours prior to screening*
- Initiation of therapy with systemic or inhaled anticholinergics within 48 hours prior to screening*
- Patients receiving cyclosporine, bromocriptine, or drugs with low therapeutic index that are mainly metabolized by CYP3A4

*Initiation of aerosolized (inhaled) anticholinergics or steroids will not be withheld to qualify a subject for the study. Once a mechanically ventilated patient has been on an anticholinergic for more than 48 hours or a steroid for more than 72 hours, he or she will no longer meet that exclusion criteria and may be included in this study with appropriate debriefing about the study by the study team to the patient or their authorized representing and obtaining informed consent.

Withdrawal of subjects:
If, for any reason, a subject or his/her legal representative chooses to discontinue involvement in the study at any time, they may do so by informing the study doctor (PI Dr. Hegde) his or her wishes. In this case, all the interventions related to the study and prospective collection of study-related data will be stopped, and the standard of care management, as determined by the Primary Team, will be resumed. Only the data that has already been prospectively collected, along with the data obtained from retrospective chart review, will be used.

If, during the trial, starting treatment with a medication that can affect bronchial secretions is indicated for a medical condition other than increased bronchial secretions, the subject will be withdrawn from the trial. These medications are as follows: inhaled bronchodilators, inhaled or systemic anticholinergics, inhaled or systemic steroids, and octreotide.

Treatment of Subjects:
Subjects in the "Routine Care" group will receive interventions as deemed necessary by the Primary Team, which should be no different from patients not participating in this study. No evidence-based guidelines have been established for management of excessive bronchial

secretions that have not responded to standard interventions, such as nebulizer treatments. Use of systemic anticholinergics (scopolamine and glycopyrrolate) and systemic steroids have been described in case reports.

Subjects in the "Octreotide" group will receive parenteral octreotide, either as intravenous infusion (preferred option) or subcutaneously (if the previous option is not feasible). The therapeutic rate of intravenous infusion is 12-25 mcg/hour. The initial rate will be 12 mcg/hr, which will be titrated up every 3 hours by 4 mcg/hr to reach the target rate of 18 mcg/hr for patient with BMI < 26, 20 mcg/hr for patients with BMI of 26-30, or 24 mcg/hr for patients with BMI > 30. The team will adjust the infusion rate based on renal/hepatic function (per recommendations of a pharmacist) and in response to side effects but will not exceed 25mcg/hr for any subject. If intravenous infusion is not feasible, octreotide will be administered subcutaneously, with daily dose (as determined above for the intravenous infusion) divided into 2 doses given every 12 hours.

Octreotide administration will be completely stopped, if a subject develops a clinically significant adverse reaction that has not responded to decreasing the infusion rate.

Assessment of Efficacy:
Baseline volume of bronchial secretions suctioned over a 24-hour period will be recorded for all subjects, and interventions prescribed by the random treatment assignment will be initiated and continued for up to 72 hours. Simultaneously, the rate of secretions will be measured and recorded (by registered nurses taking care of the patients) during each 24-hour shift. Volume of normal saline used to flush endotracheal tube will be recorded and then subtracted from the total volume found in the suction container in the end of each shift. Effectiveness of the interventions studied in this trial will be determined by comparing the percent change in the secretions rate(relative to the baseline rate) between the "Octreotide" and "Routine group" subjects, which will be the primary outcome. The secondary outcome will be the percentage of patients who were extubated within 72 hours after initiating the interventions ("Octreotide" vs "Routine").

Assessment of Safety:
The study will be performed in mechanically ventilated patients in an ICU, an environment where close monitoring of all patients in an absolute requirement. Similarly to the patients in the control arm, subjects in the treatment arm will be closely monitored for adverse reactions of octreotide. Close monitoring includes continuous and periodic monitoring of vital signs including Heart Rate, Blood Pressure and Respiratory Rate. Based on these data, as well as results of serum chemistry performed at least daily (which is part of the standard care in ICU), doses of beta-blockers, calcium channel blockers, insulin, and agents to control fluid and electrolyte balance will be adjusted, - similarly to situations when octreotide is used for other medical conditions.

Given the reported adverse reactions of octreotide, an electrocardiogram will reviewed for each subject, and patients with bradycardia and significant conduction defects will be excluded (see the exclusion criteria). During the study, vital signs will be monitored every hour, and cardiac activity will be continuously monitored by telemetry. To confirm timely assessment of safety,

the study team will ensure that the vital signs data are recorded every 4 hours in the data collection tool.
If a patient develops bradycardia (HR < 60 bpm), octreotide administration will be stopped and the patient will be withdrawn from the study. Furthermore, if a subject experiences increase in systolic BP to 180 mmHg or above, octreotide administration will be stopped and the patient will be withdrawn from the study. However, if a subject experiences increase in systolic BP by at least 40mmHg over 2 hours, the infusion rate will be decreased to 12 mcg/hr; the BP will be reassessed every hour, and the infusion rate will be titrated up as tolerated to a maximum of 25mcg. Given octreotide's effect on serum glucose level, all subject's capillary blood glucose (CBG) will be monitored every 4 hours to monitor for hyperglycemia and hypoglycemia. The glucose levels every 4 hours will be recorded in the data collection form. Subjects who are hyperglycemic and require more than 20 units of intravenous insulin per hour will be withdrawn from the study, as will subjects who experience hypoglycemia (CBG < 60 mg/dL) despite being on 5% dextrose drip.

Statistical analysis:
Data will be analyzed with the assistance of a statistician at Danbury Hospital's Department of Research and Innovation. The differences between the two groups (Routine Care vs. Octreotide) in the percentage change of rate of secretion (defined as milliliters per 24 hours) for each of the 24-hour periods as compared to the baseline 24-hour period and proportion of patients extubated within 72 hours (defined as both time to extubation AND yes/no extubated within 72 hours) will be compared. The Fisher's exact test will be used to assess statistical significance (alpha set at $p<0.05$). If the sample size allows and there are adequate cell frequencies, regression analyses will be used to assess the association between the use of Octreotide and the primary outcome variables.
Given that no previous research has been conducted to examine management of bronchorrhea resistant to conventional interventions in mechanically ventilated patients, a power calculation to estimate the sample size cannot be performed reliably. We do recognize the small sample size to be included in our study and intend for this project to serve as a pilot study that would provide some evidence-based information to guide clinicians at our institution in such situations and provide background information for further studies on a much larger scale.

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