Protocol Title: Oscillatory Positive Expiratory Pressure Devices in Acute Inpatient Treatment of Pneumonia

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Background:

Pneumonia is one of the most common health conditions leading to hospitalization today. Approximately 1.3 million people in the US are admitted to the hospital with community-acquired pneumonia (CAP) annually, with readmission rates within the first 30 days as high as 20%. In a retrospective analysis of patients with culture-confirmed bacterial pneumonia, 30-day readmission occurred in 19.3% of patients. At Norwalk Hospital, the 30-day readmission rate for patients with pneumonia is 13.1%. CAP is the sixth most common cause of death with a case-fatality rate of up to 16% for hospitalized CAP patients, and an overall 30-day mortality up to 23%. The economic burden of CAP is also high, l with a CAP cost burden estimated to be at least $13 billion in 2008 within just the Medicare population.

Antibiotics represent the mainstay of pneumonia treatment with other therapies being mostly supportive. In bacterial CAP, prompt initiation of antibiotic therapy is critical in preventing mortality however the optimal duration of antibiotic therapy in CAP is unknown. Current guidelines recommend antibiotic courses of 7 to 21 days, depending on illness severity and type of pathogen. However, adherence to guidelines is variable and physicians tend to treat longer with antibiotics, especially in elderly patients with comorbidities and patients with severe CAP. Duration of antibiotic therapy can be guided by clinical signs such as defervescence, decrease in sputum production and coughing, or improvement of general condition. There is harm associated with antibiotic usage, however, ranging from development of antibiotic resistance to antibiotic-associated diarrhea to *Clostridium Difficile* infection. Thus, strategies to reduce the duration of antibiotics are clinically important and necessary.

The mucosal lining of the respiratory tract originates from products of secretory cells interspersed among mucosal cells or within submucosal glands, and it protects the underlying mucosa from dehydration. Current understanding is that the lining is a two-fluid model in which the upper layer is a viscoelastic gel (mucus, cross-linked glycoproteins) that overlies a sol layer (serous). Sensory stimuli enhance mucus secretion and cause bronchoconstriction, responses that are usually coupled to cough and two-phase gas–liquid clearance of mucus. During times of inflammation, such as with pneumonia, mucus hypersecretion and mucus layer transport is delayed, and abnormal clearance then predominates in the smaller peripheral airways.

When treating patients with respiratory secretion problems such as pneumonia, it is advantageous to help clear the patient's lungs of the secretions as failure to clear secretions

can lead to obstruction from mucus plugging, sequestration of bacteria, ongoing fever, hypoxemia, and prolonged duration of disease, for instance. These infected secretions are best dislodged by a series of two different therapies which are combined in an oscillatory positive expiratory pressure (oPEP) device. First, a positive expiratory pressure (PEP) is exerted back into the lungs, gently increasing air pressure into the bronchi and pulmonary alveoli. This pressure prevents airway collapse by stenting the airways open, or increasing intrathoracic pressure distal to retained secretions, by collateral ventilation or by increasing functional residual capacity. Second, the application of a series of pressure waves (oscillatory vibrations) additionally provides a percussive effect, reducing the viscoelasticity of the mucus, and dislodging these secretions from the lungs so that they can be expelled. This can be accomplished with an oPEP device that uses the patient's own breathing to generate a series of pressure waves with each exhalation cycle that causes the thorax to vibrate and loosen the mucus so that it may be expelled.

Airway clearance is a strategy for treating symptoms of respiratory disorders by improving a patient’s respiratory status by enhancing mucus clearance, reducing airway resistance, enhancing gas exchange, and reducing overall work of breathing. Chest physiotherapy and airway clearance has been the mainstay of treatment and prevention of exacerbation in the cystic fibrosis (CF) population for decades, and has had its use expanded to the non-CF bronchiectasis and acute bronchiolitis populations, and in patients being mechanically ventilated. There have also been recent positive trials within the realm of chronic bronchitis and COPD as well which showed that airway clearance was beneficial in reducing the daily volume of sputum produced and increasing FEV_1.

There have been several small studies done to analyze the utility of airway clearance and its potential role in CAP. These studies have generally been small and have used a wide variety of airway clearance devices and techniques, including external chest wall physiotherapy devices and postural drainage, both now considered second line therapies for most patients. These studies have been variable in their findings and overall have not shown that airway clearance is either beneficial or harmful in CAP. The studies did show, however, that the duration of fever and hospital length of stay were both significantly decreased, suggesting the possibility of other clinically important benefits.(Ntoumenopoulos 2002; Tydeman 1989).

Objectives:

We will test our hypothesis that the use of oPEP devices, specifically the handheld Aerobika (Monaghan Medical) in this study, will result in more rapid and durable recovery in patients hospitalized with community-acquired pneumonia as measured by decreased hospital length of stay, reduced duration of fever, improvement in dyspnea, decreased duration of antibiotics, increased rate of diagnosis of the etiologic organism responsible for the pneumonia, and reduced readmission rates:

Primary outcome

1. Reduction in hospital length of stay

Secondary outcomes

1. Reduction in dyspnea by modified-Borg score
2. Reduction in duration of antibiotics
3. Reduction in duration of fever
4. Reduction in need for oxygen at hospital discharge
5. Reduction in 30-, 60-, and 90-day readmission rates
6. Diagnosis of organism by sputum
7. Transfer to the intensive care unit (ICU)

Study type: Prospective randomized controlled trial

Design:

The study investigators will perform daily screening by chart review of patients admitted to the hospital in the previous 24 hours using the ICD-10 codes as below to find appropriate patients for secondary screening:

J13 Pneumonia due to Streptococcus pneumoniae
J14 Pneumonia due to Hemophilus influenzae
J15 Bacterial pneumonia, not elsewhere classified
J16 Pneumonia due to other infectious organisms, not elsewhere classified
J17 Pneumonia in diseases classified elsewhere
J18 Pneumonia, unspecified organism
J69 Pneumonitis due to inhalation of food and vomit

A partial HIPAA waiver will be obtained for the purposes of focused screening for eligibility. If the patient is deemed eligible for the study, the study investigators will approach the hospitalist/teaching attending for collateral information and permission to approach the patient for consent. After consent is obtained, the study investigator will perform a brief patient interview to obtain information on race/ethnicity, smoking and alcohol history, to confirm past medical and medication histories, and to perform baseline assessments of dyspnea (modified BORG).

Once consent is obtained, Patients will then be randomized using block randomization. We will receive pre-made envelopes in blocks of 10 from a centralized research coordinator. Investigators performing the initial screening and enrollment will be blinded to the envelope contents until after the patient consents to participation in the study. Once the patient consents to participation, the next consecutively numbered envelope will be opened revealing the allocation to either the control or intervention group. The principal investigator will keep the envelopes secured, and will be responsible for providing each envelope to the enrolling investigator after consent has been obtained.

The intervention will consist of oPEP therapy added to standard pneumonia care (see below). “Standard pneumonia care” will not be dictated by the study protocol, but rather at the discretion of the treating clinicians. Patients who are initially admitted to the intensive care unit (ICU) will not be included in this study even when they are downgraded to general medical floors, but patients will not be excluded if they are enrolled while on the medical floors and are later upgraded to ICU level of care. Enrollment will occur Monday through Friday, thus including patients being admitted on Sunday through Friday.

Patients in the intervention group will be directed to perform the Aerobika therapy twice daily under the guidance of a study investigator for a total of at least 5 minutes per session. The study investigator will appropriately adjust the device on first use, as well as teaching the patient the correct technique for device usage. The primary patient-centered outcome will be the modified-Borg score for dyspnea which will be collected on admission, and on each subsequent morning until discharge on all enrolled patients. Patients will be encouraged to use the device on their own between the monitored sessions, as the device can safely be used multiple times daily. Patients will be surveyed each morning to self-report additional usage of the device. The device will also be available in the patient’s room for in-line use of nebulizer treatments

administered by respiratory therapists, at the discretion of the therapist. Ordering of any nebulized medications is at the discretion of the treating clinicians or respiratory therapists, the latter through a standard and general respiratory therapist-driven protocol used in our institution. Charting of any nebulizer therapy will be reviewed to assess additional use of the device as well. The intervention will continue through the duration of the patient's hospitalization, and the patient will have the option to take the device at home with them if they wish to continue using it after discharge. If patients experience intolerable dyspnea or chest tightness during use of the Aerobika, despite coaching and troubleshooting by the bedside investigator, the Aerobika session will be aborted. If the patient is unable to tolerate the therapy during three consecutive sessions, then the patient will be withdrawn from intervention.

Crossover into the Aerobika group will not be restricted if the attending physician treating the patient deems it a necessary part of the patient's care. Rates of crossover will be collected as part of study data. All analyses will be performed using intention-to-treat as well as a modified intention-to-treat method considering the intervention group to include patients randomized to intervention AND who received at least one Aerobika treatment.

Variables to be collected

Demographics: Age at admission Gender Race/ethnicity (self-reported)	Lifestyle: Smoking history (ever/current/never) Alcohol consumption frequency
Home and inpatient medications: PPI/H2-blockers Statins? Hypoglycemics/insulin Systemic steroids Inhaled medications including by nebulization Immunosuppressives	Symptoms:

Physical/Vital signs: BMI (height/weight at admission) Heart rate (daily maximum/minimum) Pulse oximetry (daily maximum/minimum, including FiO2 maximum/minimum) Temperature (daily maximum/minimum) Blood pressure (daily maximum/minimum)	Comorbidities/Past Medical History : CVA Heart disease Renal failure Cancer, active in last 6 months or not (excluding non-melanoma skin cancers) Lung disease (ie. asthma, COPD, ILD, bronchiectasis) GERD Oropharyngeal or other dysphagia
Scores: PSI - pneumonia severity index CURB65 Subjective (cough, dyspnea, mucus production) Modified-Borg score for dyspnea	

Sample size calculations

The median hospital length of stay (LOS) for Norwalk Hospital based on FY2017 data was 4.6 days (SD 3.16 days) for patients coded with a primary diagnosis of pneumonia. We will employ an effect size of 25%, powering for a reduction in LOS by 1 day.

Two independent study groups
The primary endpoint is an average LOS (continuous variable).

Sample Size	
Group 1	119
Group 2	119
Total	238

Study Parameters	
Mean LOS, group 1	4.6
Mean LOS, group 2	3.45

Patient identity will be protected through the use of the EHR, as well as by saving abstracted PHI on a password-protected, data-encrypted, secured drive managed by information

technology (IT) at Norwalk Hospital. Additional considerations include the use of REDCap, a secured research platform, for primary data collection and storage. Data will be destroyed when all analyses and publications have been completed.

Risks to patients are negligible as the intervention device is a safe, drug-free, easy to use, and non-invasive. Our exclusion criteria are focused on eliminating any individuals who would be at increased risk of adverse events from using an oPEP device, although such events are very rare. With any airway clearance modality there is the possibility of transient mild bronchospasm and hypoxemia at the initiation of the clearance which improves once the mucus is expectorated. This subtle physiologic phenomenon is typically not clinically evident nor of clinical significance, but this can be ameliorated with coaching by respiratory therapists and investigators who are all trained in the appropriate use of this device, and who are also highly trained to provide immediate care if any clinically evident events occur. The respiratory therapists are very familiar and comfortable with the Aerobika as they are currently using it with patients at Norwalk Hospital for augmentation of secretion clearance, typically in the context of bronchiectasis or COPD exacerbations.

Participation in this study should not result in any additional costs to the patient.
Potential benefits to patients include improved mucociliary clearance, reduction in length of hospitalization, duration of fever, improvement in respiratory symptom-related quality of life and duration of antibiotics, all of which have been shown to be statistically significant in previous studies, although not specific to inpatient treatment of pneumonia, as this study aims to do.

Selection and withdrawal of subjects:
Our inclusion and exclusion criteria are developed based on existing literature, the manufacturer's FDA approval, and the scope of our study.

Inclusion

1. Age 18 years or older
2. Clinical symptoms suggesting pneumonia (eg. cough, fever, pleuritic chest pain, sputum production, dyspnea)
3. Any new chest radiographic infiltrate consistent with pneumonia

Exclusion

1. Untreated or recently (within the past 90 days) treated pneumothorax
2. Active hemoptysis
3. Recent facial, oral, or skull trauma
4. Hemodynamically unstable patients
5. Severe nausea or active vomiting
6. Recent diagnosis of pneumonia prior to current inpatient encounter (within 60 days)
7. Significant cognitive impairment or psychiatric conditions that prevent ability to participate in or cooperate with oPEP use
8. Active tuberculosis or negative pressure isolation for rule out of active tuberculosis
9. Pregnancy
10. Pre-existing medical condition with a life expectancy of less than 3 months
11. Inability to form appropriate mouth seal on device (eg. due to neuromuscular disease)
12. Pre-existing active use of oPEP devices
13. Requiring >=50% FiO2 or facemask (excluding high flow NC)

Assessment of Efficacy:

This study is not designed to assess the efficacy of any drug, supplement, device, etc.

Assessment of Safety:

No known safety issues exist as no procedures will be conducted on patients for this study outside of the scope of their current use. Furthermore all medical devices in this study are FDA approved and currently being used for the indication being studied in this project.

Statistical Analysis:

Comparative statistics will be employed to determine if outcomes in the intervention (oPEP) group are statistically different from those in the control group. This will be done with the assistance of in-network statisticians as well as available statistical software.

Direct Access to Source Data Documents:

The study's Principal Investigator, primary study coordinator, and co-investigators will have access to all study data. These data will be used for study purposes only, and will be stored on a password-protected, data-encrypted, secure drive managed by IT at Norwalk Hospital. Data may be released to regulatory agencies as necessary, including the US Food and Drug

Administration, Department of Health and Human Services agencies, BRANY, the WCHN IRB, accrediting agencies, and data safety monitoring boards.

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