Official Title: Aerosolized Antibiotics in the Treatment of Ventilator Associated Pneumonia: A Pilot Study

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Aerosolized Antibiotics in the Treatment of Ventilator Associated Pneumonia: A Pilot Study

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[21]. We propose that similar responses exist in patients with ventilator-associated pneumonia (VAP) and will evaluate cytokines in both BAL and blood of patients with and without evidence of a bacterial infection.

It is also known that patients with clinical evidence of VAP never manifest evidence of a bacterial infection. This could be secondary to systemic inflammatory responses to other insults or due to the presence of viral species. By testing both culture positive and culture negative patients for evidence of viral or atypical microbial causes of pneumonia, we hope to identify potentially treatable causes of pneumonia and evaluate the effect of the concomitant non-bacterial pathogens on the ability to clear pneumonia in culture proven cases of VAP.

We propose that a prospective randomized trial needs to be performed to answer some of the questions regarding the value of aerosolized antibiotics in the treatment of ventilator associated pneumonia and to evaluate the impact of co-existing, non-bacterial pathogens and cytokines on the disease

2. Purpose and Objectives

1. To show that aerosolized antibiotics will improve clinical outcomes in ventilator associated pneumonia.
    a. The primary endpoint assessed will be recurrence.
        i. Recurrence will be defined by the CDC definition of nosocomial pneumonia (see appendix A).
    b. The CPIS (Clinical Pulmonary Infection Score) and the MDOS (Multiple Organ Dysfunction Score) will be used to monitor outcomes and clinical resolution. (see appendices B and D)
    c. Individual clinical indicators will also be recorded and used to monitor the effect of aerosolized antibiotics (temperature, leukocyte count, chest radiograph appearance, PaO2/FiO2 ratio, mechanical ventilation status, vital signs)
2. To evaluate Cytokine levels for patients with and without microbiologic evidence of respiratory tract infection.
3. To evaluate viral presence for patients with and without microbiologic evidence of respiratory tract infection.

3. Methods

Clinical Work

Mechanically ventilated patients in the Surgical, Medical, Neuro-Surgical, and Cardiovascular Intensive Care Units at Miami Valley Hospital will be eligible to participate in this study. Patients will be considered eligible for study enrollment if the primary team suspects a respiratory infection and plans on performing a bronchoscopy with broncheoalveloar lavage (BAL) or protected catheter specimen (Combicath) to confirm the diagnosis of ventilator associated pneumonia. At that time, the patient's legally authorized representative (LAR) will be approached to inform them of the study and obtain consent to permit patient enrollment. Consent will be obtained prior to administration of aerosolized antibiotics (see appendix E) either via telephone or in person. If consent is obtained via phone (script attached),

Department will cover the cost of antibiotics and other materials/supplies to carry out the study (see appendix G).

Translational Work

The culture effluent from selected samples will also be evaluated for the presence of viruses and a spectrum of human cytokines known and not known to be associated with local and systemic inflammation (see appendix F). All the specimens will be taken at time of screening after informed consent is obtained. However, only patients who have a positive bacterial culture ($>10^4$ CFU/ml) will be eligible to receive the drug/placebo. The specimens obtained from patients who screened positive but were microbiologically negative ($<10^4$ CFU per ml) will be used as controls for the translational aspect of the study, which would include viral and inflammatory mediator analysis. The selection of specimens to be used will be evaluated as detailed in Appendix E. Fifty culture specimens that are not positive for bacteria at a concentration of $<10^4$ CFU per ml (controls) will be compared to the culture effluent 25 specimens from those patients found to have bacterial counts $>10^4$ CFU/ml. This ratio provides a 2:1 comparison for the purposes of analysis. For the purposes of cytokine analysis, blood samples will be analyzed from the 50 controls, which will be drawn prior to initiation of aerosolized antibiotics. Blood sample analysis of cytokines will also be done on half of the culture positive patients (n=26) at time of culture collection and 7 days after treatment to assess any potential treatment effect. Of the cases selected, 13 will come from the drug treatment group and 13 will come from the placebo group.

Viral PCR analysis of the respiratory culture specimens will be performed at MVH at no cost to the patient unless clinically indicated. The cytokine analysis will be done using the (Bio-Rad Cytokine Group I). Specimens for cytokine analysis will be maintained at -80 C until they are analyzed. Cytokine testing will be done at Wright State University.

Primary Outcome: Treatment Failure

- Treatment failure is defined by persistence or recurrence of nosocomial pneumonia, as defined below.
- Recurrence will be defined microbiologically after a second specimen (BAL or combicath) reveals at least once bacterial species growing at concentrations $>10^4$ organisms during the time period from 9-21 days after initiating antibiotic therapy. If the patient does not require re-intubation, then a sputum sample will be used along with the CDC definition (appendix A) to establish the existence of a recurrent nosocomial pneumonia.

be used for analysis. Combicath specimen will be obtained in accordance with institutional respiratory therapy protocols. Those patients whose cultures show greater than 10^4 CFU/ml will be retained in the study for an analysis. The goal is to enroll 25 patients in each arm (placebo and treatment arm) of the study.

Treatment with aerosolized antibiotic will be for 7 days, but may be continued for longer if deemed necessary by the primary treating team. If continued, aerosolized antibiotics will be discontinued when intravenous antibiotic therapy is discontinued. This will be considered persistent nosocomial pneumonia. If continuation is deemed necessary by the treatment team. then an additional BAL or combicath specimen should be obtained for analysis to confirm microbiologic persistence of disease. Blood samples will also be drawn from the patients. The respiratory specimens and the blood specimens will be analyzed for inflammatory mediators. The respiratory specimens will also be analyzed for the presence of viral nucleic acid by PCR analysis. Of the patients retained in the treatment or the placebo arms for further analysis, their IV and aerosolized antibiotic therapy will be tailored appropriately based on the Species identified in the final culture. At post treatment day number seven, patients in each arm will have their blood drawn for additional cytokine analysis. Patients deemed to have persistent disease will have repeat respiratory cultures obtained in accordance with methods outlines in this protocol.

Study Population:

The population will consist of patients admitted to the Surgical, Medical, Neurology, and Cardiovascular Intensive Care Units at Miami Valley Hospital. When patients are suspected of having a ventilator associated pneumonia and the critical care team plans to perform a bronchoscopy with BAL or combicath, they will be eligible for study recruitment.

Screening Criteria: Intubated >/= 48 hours and meets ONE of the following screening criteria:

1. CPIS >/= 6
   OR
2. Suspected VAP with planned bronchoscopy and BAL

Inclusion criteria:

1. CPIS >/= 6
2. Intubated >/= 48 hours
3. Screened for possible eligibility
4. Bronchoscopy and BAL or combicath performed
5. Started on empiric IV and inhaled antibiotics after BAL or combicath for suspected VAP
6. > 10^4 CFU on BAL

Possible benefits of participating in this study include more rapid resolution of ventilator associated pneumonia and lower recurrence of nosocomial pulmonary infection.

6. Risks to Subjects:

This study is associated with some risks to the patients as describe below. The patient will be receiving IV antibiotics (standard of care), and will be given aerosolized antibiotics or aerosolized saline (placebo) as an adjunctive therapy.

There are risks to taking part in this research study. One risk is that you may have side effects secondary to antibiotic use while on the study. Side effects can range from mild to serious. Serious side effects are those that may require hospitalization, are life threatening or potentially fatal. The frequency that people experience a certain side effect can range from many (likely), few (less likely), or rare. Side effects from this study will usually resolve after cessation of the aerosolized antibiotic. Here are the risks of specific study antibiotics:

- Linezolid: allergic reaction, low blood cell counts, low platelets, changes in vision, changes in sensation, seizures, diarrhea, colon infection
- Piperacillin/tazobactam: allergic reaction, skin rash or blisters, diarrhea, colon infection, low blood cell counts, bleeding, low potassium levels, seizures
- Vancomycin: allergic reaction, low blood pressure, skin rash or blistering, kidney injury, hearing changes, low blood cell counts, diarrhea, colon infection, inflammation of the veins
- Tobramycin: changes in hearing, balance disturbance, kidney injury, allergic reaction, skin rash or blistering, kidney injury, dizziness, hearing changes

All patients participating in this study will be carefully monitored for any side effects. However, the study doctors may not know all of the possible side effects.

Risks specific to bronchoscopy include a minor drop in oxygen level, minor bleeding, pneumothorax, infection, fever.

Risks specific to aerosolized study antibiotics or placebo include:

- Allergic reaction, including but not limited to rash, edema, or anaphylaxis
- Adverse reaction to aerosolized study antibiotics or placebo including bronchospasm, bronchoconstriction, lung inflammation or irritation, wheezing, or other breathing difficulty

Justification of Number of Subjects:

This is a pilot study and as such, an a priori decision to enroll twenty five patients in each arm (placebo and treatment arm) was made (i.e., total of 50 subjects). However, as mentioned above, the specimens obtained from patients who screened positive but were microbiologically negative will be used as controls for the

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- Consolidation
- Cavitation
- Pneumatoceles in infants </= 1 year old

Appendix C

APACHE II Score [18]

THE APACHE II SEVERITY OF DISEASE CLASSIFICATION SYSTEM

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
	+4	+3	+2	+1	0	+1	+2	+3	+4
TEMPERATURE — rectal (°C)	≥41°	39°-40.9°		38.5°-38.9°	36°-38.4°	34°-35.9°	32°-33.9°	30°-31.9°	≤29.9°
MEAN ARTERIAL PRESSURE — mm Hg	≥160	130-159	110-129		70-109		50-69		≤49
HEART RATE (ventricular response)	≥180	140-179	110-139		70-109		55-69	40-54	≤39
RESPIRATORY RATE — (non-ventilated or ventilated)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
OXYGENATION: A-aDO_2 or PaO_2 (mm Hg) a. FiO_2 ≥ 0.5 record A-aDO_2	≥500	350-499	200-349		<200				
b. FiO_2 < 0.5 record only PaO_2					PO_2 > 70	PO_2 61-70		PO_2 55-60	PO_2 < 55
ARTERIAL pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	< 7.15
SERUM SODIUM (mMol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
SERUM POTASSIUM (mMol/L)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
SERUM CREATININE (mg/100 ml) (Double point score for acute renal failure)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		< 0.6		
HEMATOCRIT (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
WHITE BLOOD COUNT (total/mm3) (in 1,000s)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
GLASGOW COMA SCORE (GCS): Score = 15 minus actual GCS									
[A] Total ACUTE PHYSIOLOGY SCORE (APS): Sum of the 12 individual variable points									
Serum HCO_3 (venous-mMol/L) (Not preferred, use if no ABGs)	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15

[B] AGE POINTS: Assign points to age as follows:

AGE(yrs)	Points
≤44	0
45-54	2
55-64	3
65-74	5
≥75	6

[C] CHRONIC HEALTH POINTS

If the patient has a history of severe organ system insufficiency or is immuno-compromised assign points as follows:

a. for nonoperative or emergency postoperative patients — 5 points
or
b. for elective postoperative patients — 2 points

DEFINITIONS

Organ insufficiency or immuno-compromised state must have been evident prior to this hospital admission and conform to the following criteria:

LIVER: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.

CARDIOVASCULAR: New York Heart Association Class IV.

RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40mmHg), or respirator dependency.

RENAL: Receiving chronic dialysis.

IMMUNO-COMPROMISED: The patient has received therapy that suppresses resistance to infection, e.g., immuno-suppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS.

APACHE II SCORE

Sum of [A] + [B] + [C] :

[A] APS points _____

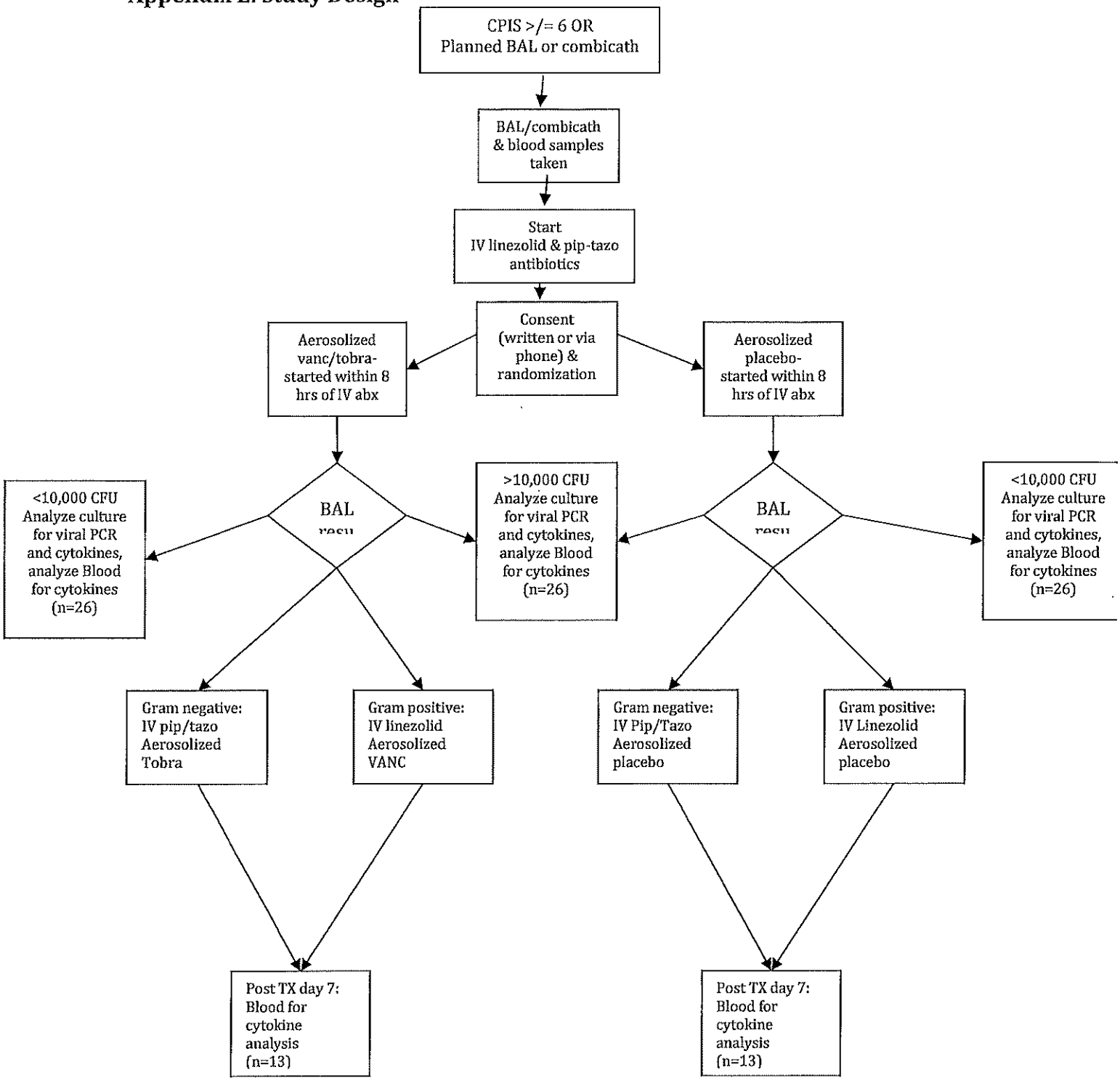
[B] Age points _____

[C] Chronic Health points _____

Total APACHE II _____

FIG. 1. The APACHE II severity of disease classification system.

Appendix E: Study Design



Appendix G: Cost of Clinical Work

Antibiotic	Price per patient for 7 day course	Cost for 25 patients
Vancomycin 125mg q 8hr – for inhalation	$14.14	$353.50
Tobramycin 300mg q 12hr – for inhalation	$231.63	$5,790.75
Piperacillin/Tazobactam 3.375gm IV q 8 hr	Standard of care	Standard of care
Linezolid 600mg IV q 12hr	Standard of care	Standard of care