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IRB Proposal

Title: The Unclear Necessity of Antibiotics in Treatment of HIV Positive Patient with Presumed Uncomplicated Acute Bronchitis

A. Study Purpose and Rationale:

In the immunocompetent patient population without underlying lung disease, acute bronchitis is frequently encountered in both an outpatient and emergency department setting, and is often treated with antibiotics, despite the knowledge that this entity is most commonly caused by a virus(4). Case series performed to identify the microbial agent responsible for acute bronchitis in immunocompetent adults have shown that the usual pathogens are viral infections, including influenza A and B, parainfluenza, coronavirius (types 1-3), rhinovirus, respiratory syncytial virus, and human metapneuomovirus (6). Despite this knowledge, doctors often remain concerned that there is a bacterial etiology to the patient's presentation, with specific concern for bacteria that are the common causes of bacterial pneumonia. However, there is no data to support the use of antibiotics in the treatment of uncomplicated acute bronchitis, with most trials showing no benefit to antibiotic therapy (1). This has led to campaigns by the Centers for Disease Control and Prevention (CDC) to avoid antibiotic use in this setting (5).

Patients with HIV and without underlying lung disease, also frequently present with signs and symptoms of acute bronchitis and given their immunosuppressed state, the inclination is also to treat them with antibiotics used for community acquired pneumonia (CAP), as also occurs in an immunocompetent patient population. In fact, the inclination to treat them with antibiotics is probably much greater given their immunosuppressed state. However, there has been no case series performed to identify the microbial pathogens responsible for acute bronchitis in HIV positive patients, as has been performed in immunocompetent patients. It is presumed most likely to be viral in origin as well. This presumption is partially supported by the knowledge that the most common pathogens for CAP in the HIV population are similar to that occurring in the HIV negative population, showing that the same microbial agents are likely responsible for the same disease processes in both patient populations (7).

At Columbia Presbyterian Medical Center's (CPMC) Emergency Department, any patient that presents with a known diagnosis of HIV with a complaint of cough and fever and found to have a normal chest x-ray, will likely receive antibiotics for CAP, namely Ceftriaxone and Azithromycin or Levofloxacin in the penicillin allergic patient, and be admitted for further management on the Infectious Diseases Service, which is staffed by medicine residents of the Internal Medicine Residency Training Program. Once admitted to the hospital floors, a decision is made by the house staff to continue or discontinue antibiotic therapy. However, antibiotic therapy is often continued since it was started initially in the Emergency Department with plan for the patient to receive a short course of therapy (usually a total of five days). Given the proposed etiology of the patient's presentation of uncomplicated acute bronchitis is a virus, antibiotic therapy is presumably unnecessary and also not without adverse consequences, such as allergic reactions, pseudomembranous colitis, the possible side effects of each individual antibiotic, and on a broader public health scale, the development of antibiotic resistant organisms. Therefore, I propose, as in the studies performed on immunocompetent patients with acute bronchitis, antibiotic therapy versus no antibiotic therapy will have no effect on clinical outcomes, specifically with regards to the duration of hospital stay of this HIV positive patient population.

B. Methods
Study Design:

This research will be constructed as a randomized, prospective, double blinded placebo controlled trial. Subjects will be randomized into a standard treatment group (control group) that receives antibiotics and a group that does not receive antibiotics.

Men and woman greater than or equal to 18 years of age with a known diagnosis of HIV who present to the emergency department at Columbia Presbyterian Medical Center with complaints of cough, fever (T>100.4 but less than 101.5F) and have a normal chest x-ray will be eligible for participation. A detailed history and physical examination will be performed on the subjects. Subjects will be eliminated based on their medical history if they have known underlying lung disease, such as COPD, bronchiectasis, recurrent episodes of bronchitis (three or more episodes per year), history of a tracheostomy or if they have underlying heart disease (any prior hospitalization for myocardial infarction, symptoms of unstable angina, or stage III or IV NYHA Heart Failure), or if they have localizing symptoms of infection (altered mental status, diarrhea, cellulitis, or abdominal pain). Subjects will be eliminated based on physical examination if their heart rate is greater than 100, respiratory rate is greater than 24, pulse oximetry less than 95%, mean arterial blood pressure is less than 65mmHg or if they have any other localizing sources of infection on physical examination, such as cellulitis, abdominal pain, CVA tenderness.

All subjects will undergo the standard workup for a patient with a fever, including chest x-ray, two sets of blood cultures, a sputum culture, and a urinalysis. Patients with a CD4 count less than 200 will also likely receive additional workup including but not limited to serum cryptococcal antigen, mycobacterial isolators, urinary Histoplasma antigen, CMV PCR, and possibly a lumbar puncture. The measurement of an LDH level will also be helpful in this patient population given the possibility for PCP exists. Subjects will be eliminated if their urinalysis is positive for evidence of infection (positive leukocyte esterase), if any abnormalities are found on chest x-ray, or if their LDH is >200. If an ABG is performed and an A-a gradient is greater than 20 mmHg or PaO2<70 mmHg, the patient will be excluded from the study.

Once the patients are randomized into the antibiotic and no antibiotic group, the pharmacy will release the appropriate antibiotic or its placebo counterpart: intravenous saline in the same quantity and packaging as the antibiotic. The patients and the physicians caring for the patients will not be aware of which arm the patients are randomized into. However, if the patient does not clinically improve or clinically worsens, or if the blood or sputum culture returns positive for a bacterial pathogen, and knowledge of which treatment arm the patient is in affects the further treatment of the patient, i.e. the need to broaden antibiotic coverage, the physician may call the pharmacy at any time to find out which group the patient is in to ensure the safety of the patient. All patients who crossover into the other arm of the study will be analyzed based on the intention to treat principle. All decisions from the point of admission to the Infectious Diseases Team will then be made by the medicine house staff with no input from any person involved in this study. Therefore, the medicine house staff and not the principle investigator or the research assistants will determine when the patient will be discharged from the hospital.

The primary outcome will be the length of hospital stay. A secondary outcome will be the time (in days) from admission that the patient is afebrile for at least 24 hours, as this is the time period in which the patient should be allowed to be discharged, pending no social issues or unforeseen circumstances that would keep the patient in the hospital. We will also examine the percentage of patients who crossover into the antibiotics group based on CD4 count, within three separate subgroups: CD4>500, CD4 200-500 and CD4<200, since the incidence of pneumonia increases exponentially as the CD4 count drops.

We hypothesize that there will be no difference in length of hospital stay between the group who receives antibiotics versus the group that does not receives antibiotics.

Power Analysis:

An unpaired t-test was utilized for power analysis in this study. Although there are no clear data for expected length of hospital stay in this patient population, most HIV patients with the presenting symptoms of fever, cough and normal chest x-ray stay for between 2 and 7 days. The standard deviation is likely to be

approximately one and a half day, with approximately 70% of the patients falling between 3 and 6 days of hospitalization.

Using the unpaired t-test and the effect size of one half day to test for non-inferiority between the antibiotic and the no antibiotic groups, this corresponds to approximately 100 patients needed in each cohort for 80% power, testing at p=0.05. A gross estimate of about 3-5 patient's meeting the criteria to be included in this patient study are admitted to CPMC each week. Therefore, the study would have to take place over about a two year period to enroll enough patients (accounting for patient refusal to participate).

Statistical Analysis: Means and standard deviations will be calculated for length of hospital stay for patients in both study groups. These will be calculated in days. The student's unpaired t-test will utilize the means, standard deviations, and sample sizes of the study groups in order to report a p value. Statistical significance is set at $p<0.05$.

C. Study Procedures: N/A

D. Study Drugs: No study drugs will be employed apart from conventional antibiotics and other medications used commonly in the treatment of CAP at Columbia Presbyterian Medical Center, such as Ceftriaxone and Azithromycin or Levofloxacin therapy if the patient is penicillin allergic. These medications would be used in the absence of this research protocol and their risks are consequently not altered by the implementation of the study. The placebo drug consists of intravenous saline in the same dose as the antibiotic that would be used, and therefore should not exceed 100cc per dose, thereby limiting side effects of volume overload.

E. Medical Device: None.

F. Study Questionnaires: None.

G. Study Subjects: The inclusion and exclusion characteristics of study subjects are as listed above.

H. Recruitment of Subjects: All patients admitted through the adult emergency department who have HIV and meet the criteria listed above will be considered for the study. The ED physician will then notify the principle investigator of the patient's eligibility. The principle investigator will then contact one of the research assistants, and if deemed eligible, will discuss the study with the patient. The research assistant will obtain consent to participate in this study from all willing participants after risks, benefits and alternatives are explained. Patients will be excluded from the study if severely intoxicated. Otherwise, if patients are deemed competent and found to have capacity to make decisions, consent will be obtained from all willing individuals.

Although, CPMC policy requires that the patient's primary physician agree that the patient is suitable for this study and ascertain willingness of the patient to participate prior to any approach by the investigator, this requirement will make it impossible to conduct this study. Many HIV patients who present to the emergency department at CPMC may not have a primary care physician, or if they do, contacting them in an appropriate period of time given the emergency department setting, will be difficult to perform. Since any patient with a presumed or admitting diagnosis of uncomplicated acute bronchitis is presumed to have a viral cause to their presentation, antibiotics are technically unnecessary and therefore, no ethical dilemma is involved by denying antibiotic therapy.

I. Confidentiality of Study Data: All study data will be coded using a unique code number to ensure confidentiality to all trial participants. The data will be stored in a secure location, which will be accessible only to investigators, as per IRB regulations.

J. Potential Conflict of Interest: None of the study investigators have a financial interest or monetary affiliation with any pharmacological company that manufactures antibiotics.

K. Location of the Study: Adult Emergency Department, New York Presbyterian Hospital, and Milstein Hospital, all part of Columbia University Medical Center – New York City, New York

L. Potential Risks: Patients randomized to the non-antibiotic group who eventually demonstrate a bacterial cause of their presenting symptoms (positive blood or sputum cultures) may clinically worsen or not improve from their initial presentation, thereby necessitating antibiotic therapy at a later point than those initially randomized to the antibiotic group. This will likely result in a longer hospital stays for those patients. The possibility of the development of sepsis from an untreated bacterial infection does exist, though by using the above exclusion criteria, patients who would be most adversely affected by missing a bacterial cause and thereby go on to development life threatening sepsis would not be enrolled in this study.

M. Potential Benefits: Patients enrolled in the non-antibiotic arm of the study will avoid possible allergic reactions to the antibiotics, any side effects associated with the specific antibiotics uses, or pseudomembranous colitis. Larger long term benefits also include the development of less resistant bacterial organisms if antibiotics are not used. If there shown to be no difference between either treatment arms, avoiding antibiotic use in the future in this setting can result in a monetary saving for the hospital and/or patient.

N. Alternative Therapies: The patients who do not receive antibiotics will receive a placebo counterpart: intravenous saline in the same quantity and packaging as the antibiotics being given in the antibiotic group.

O. Compensation of Subjects: None.

P. Cost to Subjects: None.

Q. Minors as Research Subjects: Only adults >18years of age will be eligible to participate in this study.

R. Radiation or Radioactive Substances: None.

References

1. Bartlett, John. Acute bronchitis. UpToDate, www.uptodate.com, Jan 2007

2. Beck, J, Rosen, M, and Peavy, H. Pulmonary Complications of HIV Infections. NHLBI Workshop Summary. Am J Respir Crit Care Med Vol 164:2120-2126, 2001.

3. Boyton, R. Infectious lung complications in patients with HIV/AIDS. Current Opinion in Pulmonary Medicine. 11:203-207, 2005.

4. Gonzales, R, Steiner, JF, Lum, A, Barrett, PH Jr. Decreasing antibiotic use in ambulatory practice: impact of a multidimensional intervention on the treatment of uncomplicated acute bronchitis in adults. JAMA 1999; 281:1512.

5. Gonzales, R, Bartlett, JG, Besser, RE, et al. Principles of appropriate antibiotic use for treatment of uncomplicated acute bronchitis: background. Ann Intern Med 2001; 134:521.

6. Gonzales, R, Sande, M. What will it take to stop physicians from prescribing antibiotics in acute bronchitis? Lancet 1995; 345:665.

7. Hirschtick, R, Glassroth, J, Jordan, M, et. al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. N Engl J Med 1995: 333:845.

8. Lucas, Gregory. Bacterial pulmonary infections in HIV-infected patients. UpToDate. www.uptodate.com, Sept 2007

9. Stover, Diane, Approach to the HIV-infected patient with pulmonary symptoms. UpToDate, www.uptodate.com, April 2007

10. Wolff, A, O'Donnell, A. HIV-related pulmonary infections: a review of the recent literature. Current Opinion in Pulmonary Medicine 9:210-214, 2003.