Empiric Treatment of Community-Acquired Pneumonia in the Outpatient Setting: A Prospective, Double-blind Randomized Trial

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A. Study Purpose and Rationale

Community-Acquired Pneumonia (CAP) is a common problem in the United States, with estimates of between 2 and 4 million cases annually, of which approximately 3/4 are treated as outpatients.[i,ii] Therapy in this larger group is largely empiric, and is not based on the results of blood or sputum cultures. However, epidemiological data has consistently indicated that any antibiotic regimen should cover the most common causes of CAP – Streptococcus Pneumoniae, Hemophilus influenzae, Mycoplasma pneumoniae, Chlamydia species, and Legionella species. Current guidelines from the Infectious Disease Society of America recommend the use of either a macrolide such as azithromycin or an anti-pneumococcal fluoroquinolone like levofloxacin for all cases, but voice no preference. [iii] However, the American Thoracic Society consensus guidelines recommend that macrolides be used as first line agents in low-risk patients with pneumonia, given the possibility that overuse of fluoroquinolones could engender increased pneumococcal resistance.[iv]

Numerous studies have been conducted which examine the efficacy of fluoroquinolones and macrolides in community-acquired pneumonia. Levofloxacin has been reported to have about 97% efficacy (in a study comparing it to ceftriaxone and/or cefuroxime in the treatment of hospitalized patients with CAP), and has been noted by the manufacturer to have 93-95% efficacy in all cases of CAP.[v] Azithromycin has excellent efficacy in CAP, especially in those cases most likely due to "atypical" organisms. An open, randomized study of a 3-day course of azithromycin (vs. a 10 day course of roxithromycin) showed clinical cure rates of 99%. "Atypical" organisms were suspected in that study because the patients had chest radiographs showing diffuse interstitial patterns. Those suspicions were confirmed by serologic analysis indicating that the majority had mycoplasma pneumoniae and chlamydia species. It also good success in CAP overall, but its success in lobar outpatient pneumonia has not been studied extensively.[vi] Studies directly comparing fluoroquinolones and macrolides have shown conflicting results, and cannot be generalized to the overall outpatient population. A comparison of grepafloxacin (since voluntarily withdrawn by its manufacturer) and clarithromycin showed equivalent efficacy of about 90%.[vii] Another study compared sparfloxacin and roxithromycin and clearly demonstrated the fluoroquinolone's superior efficacy (82% vs. 72%).[viii] The latter study's relevance to the outpatient population is unclear, as the study population included a mixture of inpatients (75%) and outpatients (25%).

No randomized trial has directly compared two antibiotics, levofloxacin and azithromycin, that are commonly used in the treatment of CAP. Each is thought to have good efficacy in CAP, though levofloxacin may be superior. As detailed above, the treatment of choice for atypical pneumonia (as seen on radiographs) would appear to be azithromycin, given its extremely good cure rate. This study proposes to compare the efficacy of these two medications in the treatment of CAP in low-risk outpatients who have lobar consolidation on chest radiograph. Although the use of levofloxacin risks the generation of increased pneumococcal resistance to fluoroquinolones, this study hypothesizes that levofloxacin will have sufficiently greater efficacy (10% ARR) as to recommend it as first line therapy for outpatients with CAP and lobar consolidation.

B. Study Design and Statistical Analysis

The trial will be a randomized, prospective, double-blind trial comparing two treatments for lobar community-acquired pneumonia. The patients will be randomized according to a stratified randomization plan which will assign equal numbers of patients from two different age groups (50-70 years and 21 - 50 years) to two parallel study arms. One arm will use a 5-day treatment course of azithromycin (500 mg by mouth daily for 5 days). The second arm will use a 10-day treatment course of Levofloxacin (500 mg by mouth daily for 10 days).

- The primary endpoint will be treatment success, as defined as clinical improvement at 4 and 10 days AND clinical cure at 30 days without the need for additional antibiotics at any point or need for hospitalization. The outcomes will be analyzed using a Chi-square test. Given prior data on the efficacy of the two drugs, levofloxacin is estimated to have an absolute risk reduction of ~10% for the primary end point. A 10 % ARR would also be needed to justify the use of levofloxacin, given the risk of creating more resistant organisms. To detect this difference with a p value of .05 and power of 80%, the following equation was used to calculate the sample size: $N = 8(p1q1 + p2q2)/effect^2 + 2/effect + 2$. In this study $n = 8(.95*.05 + .85*.15)/.01 + 2/.1 + 2 = 162$ subjects in each arm.

- The secondary end point will be the composite of hospitalization and overall mortality. Subgroup analysis will be performed on patients with s. pneumoniae infection (as shown by positive blood cultures, sputum gram stain with lancet-shaped gram-positive diplococci, or by urinary antigen) and on patients with penicillin resistant pneumococcus, (as demonstrated by culture data). In addition, subgroup analysis will also be performed comparing the difference between the two age groups (50 – 70 years and 21-50 years).

C. Study Procedure

Eligible patients will have peripheral blood (2 samples) and sputum sent for culture and sensitivity. The patient will have urine sent for Legionella antigen and S. pneumoniae antigen. The patient will then receive the study medication and one reusable thermometer, with instruction to measure his or her temperature every 8 hours for 4 days, or with symptoms of fever or chills. The patient will receive follow-up via telephone at 4 days, with inquiries as to presenting lower respiratory tract symptoms (cough, shortness of breath, or new sputum production) and as to fever (as measured by the patient.) Clinical improvement at this stage is defined by absence of fever. Other symptoms should not have worsened. The patient will be seen by a physician in 10 days and evaluated for complete lack of fever and for at least partial resolution of lower tract symptoms. (This represents clinical improvement.) The same physician will evaluate the patient at 30 days for lack of fever and complete resolution of symptoms (which represents clinical cure). The patient will be assessed at each point (4 days, 10 days and 30 days) for failure to meet each goal. If treatment failure is present, then results of blood cultures will be utilized in selecting appropriate new antibiotics.

D. Study Drugs.

Levofloxacin 500mg by mouth for 10 days. Azithromycin 500mg by mouth for 5 days. Both drugs are FDA approved for the treatment of community-acquired pneumonia.

E. Medical Devices:

Standard reusable oral thermometer.

F. Study Questionnaires:

None.

G. Study Subjects:

All adult patients in all New York-Presbyterian Emergency Departments and selected other Emergency Departments presenting with community-acquired pneumonia (as defined below) and suitable for discharge on outpatient oral therapy (as defined in the exclusion criteria).

Inclusion criteria:

1. Onset of Lower Respiratory Tract Symptoms (Cough, new sputum production OR dyspnea) less than 2 weeks ago.
2. Fever (at least one temperature greater than 101 degrees F, either measured at home or in the Emergency Dept.)
3. CXR with single lobe consolidation.

Exclusion Criteria:

1. CXR with diffuse interstitial infiltrate consistent with "atypical" pneumonia or multilobar pneumonia.
2. PORT Score >70.[ix] In addition, other high-risk patients (as defined in the PORT system as follows) will be excluded:
3. Neoplastic Disease: Any cancer except basal or squamous cell cancer of the skin that was active at the time of presentation or diagnosed within 1 year of presentation.
4. Liver Disease: a clinical or histological diagnosis of cirrhosis or other form of chronic liver disease such as chronic active hepatitis.
5. Systolic or diastolic ventricular dysfunction documented by history and physical examination, echocardiography, MUGA scanning, or left ventriculography.
6. A clinical diagnosis of stroke, transient ischemic attack, or stroke documented by MRI or computed axial tomography.
7. Significant renal disease as defined by Creatinine >2.
8. Known HIV +
9. Hospitalization within 1 month of randomization.
10. Residence in a chronic care facility.
11. Treatment with either medication within one month of randomization.
12. Evidence for an additional source of infection outside of the respiratory tract.
13. Age < 21 years
14. Inability to tolerate oral medications
15. Inability to be contacted by telephone OR unavailable for follow up in clinic.

H. Recruitment of Subjects

A study coordinator will be available for recruitment of subjects. The coordinator may be contacted if a provider identifies a potential subject. All subjects must be able to understand the risks and benefits of the study and give informed consent for their participation. It is anticipated that based on the catchment population of the New-York Presbyterian Medical Center, equal numbers of women and men will be enrolled. In addition, the number of ethnic minorities included in the study will likely be higher than in the general U.S. population.

I. Confidentiality of Study Data

All study subjects will be assigned a unique study identification number for use in data recording and processing. Study investigators alone will have access to further identifying characteristics.

J. Potential Conflicts of Interest

None.

K. Location of the Study

Though New-York Presbyterian Medical Center will be the primary site, several other sites will need to be utilized to ensure that the results are valid for sites with different antibiotic resistance patterns.

L. Potential Risks

This study seeks to compare the efficacy of two drugs in the treatment of community-acquired pneumonia. The potential risk is associated with azithromycin is a greater risk of treatment failure, which could entail a greater mortality rate. The risks associated with the use of levofloxacin include treatment failure and the generation of fluoroquinolone-resistant pneumococcus.

M. Potential Benefits

The potential benefits include close follow-up, and potential changes in therapy based on culture data (which is not normally utilized in the treatment of outpatients).

N. Alternative Therapies

Currently both therapies utilized are approved for the treatment of CAP. Alternative drugs such as clarithromycin, erythromycin, gatifloxacin offer no additional advantages.

O. Compensation to Subjects:

None.

P. Costs to Subjects

None.

Q. Minors as Research Subjects

No minors will be involved as study subjects.

R. Radiation or Radioactive Substances:

None.

S. References

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