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There is no mortality benefit to using quinolones instead of azithromycin for Legionella pneumonia

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ABSTRACT A critical appraisal and clinical application of Gershengorn HB, Keene A, Dzierba AL, Wunsch H. The association of antibiotic treatment regimen and hospital mortality in patients hospitalized with *Legionella* pneumonia. *Clinical Infectious Diseases*. 2015;60(11):e66-e79. doi: 10.1093/cid/civ157

Keywords: *Legionella pneumonia, antibiotic therapy*

Clinical Context

A 37-year-old female patient with HIV presented to the emergency department complaining of fatigue, chest pain, and cough productive of blood streaked sputum. She was taking combination emtricitabine/tenofovir and dolutegravir for HIV, although she admitted to missing doses, and her last CD4 count two months prior to presentation was 297. She was diagnosed with community acquired *Legionella pneumophila* pneumonia by *Legionella* urine antigen testing. The patient was given an initial dose of azithromycin by the emergency physician to cover *Legionella* pneumonia and was admitted to the medicine team. Infectious diseases was consulted and recommended switching antibiotic treatment to moxifloxacin, although a specific reason was not given. The patient subsequently experienced dizziness and nausea that she attributed to the new antibiotic. Due to this adverse effect, and at the patient's request, the primary team considered discontinuing moxifloxacin and restarting treatment with azithromycin.

Clinical Question

Is azithromycin as effective as fluoroquinolones for treating community acquired *Legionella pneumophila* pneumonia?

Research Article

Gershengorn HB, Keene A, Dzierba AL, Wunsch H. The association of antibiotic treatment regimen and hospital mortality in patients hospitalized with *Legionella* pneumonia. *Clinical Infectious Diseases*. 2015;60(11):e66-e79. doi: 10.1093/cid/civ157.

Related Literature

The clinical question led to a search for "Legionella pneumonia" on Up-to-Date® and an article titled "Treatment and prevention of Legionella infection" that stated there is a lack of randomized control trial based evidence for choosing between these two classes of drugs. This article, however, presented some available evidence and contained five relevant citations, one of which was for the

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Gershengorn study that is the subject of this critical appraisal.[1] The other four studies[2-5] were not chosen for this appraisal, or for primary consideration in answering the clinical question, for several reasons. One reason is that they were published in 2005 or 2007. More recently published evidence was sought to aid in answering the clinical question. These studies had relatively small sample sizes with the largest being 292 patients.[2] A cohort study for our clinical problem would ideally have a larger number of patients studied. A final point against the other four studies from Up-to-Date® is that, when comparing macrolides to fluoroquinolones, the macrolides used were erythromycin or clarithromycin,[2-5] whereas the macrolide in current practice is usually azithromycin.

I examined the MeSH of the Gershengorn study and selected "Legionellosis/drug therapy" [MAJR], which resulted in 275 citations when used in the next PubMed search. I reviewed the abstracts from this section and found a number of relevant articles,[1-8,10] including two meta-analyses.[6,7] These were reviewed for relevant literature, yielding the same articles viewed before, as well as a CAP study that analyzed only 39 patients.[8] A Google search for articles which had cited the Gershengorn et al. study revealed a recent retrospective study by Cecchini et al. that evaluated antimicrobial therapy Legionnaires' disease patients admitted to the ICU and found a benefit of fluoroquinolone therapy.[9] This study was not chosen because of its smaller sample size (211), it only studied ICU patients, and it compared outcomes of different antimicrobial regimens, including combination therapy.[9]

The final step in searching for relevant literature was a review of the Infectious Diseases Society of America guidelines for community acquired pneumonia.[10] These guidelines cite Plouffe et al. as evidence for azithromycin efficacy against Legionella pneumonia.[11] They also cite the study by Sabría et al. as support for considering fluoroquinolones over macrolides in patients with persistent fever, however this study used erythromycin for comparison with fluoroquinolones rather than azithromycin.[4] The guidelines contained no reference to any studies comparing azithromycin with quinolones.

The research article chosen for appraisal and application to our clinical problem was an archival cohort analysis that included 3152 patients[1] hospitalized with Legionella pneumonia. This study was especially applicable to our clinical scenario because azithromycin was the macrolide used. This article best fits the clinical question because it is the most recent research found that uses a large sample size, compares the two classes of antibiotics for the treatment of Legionella pneumonia, and evaluates results using the primary outcome of hospital mortality with added benefit of evaluating hospital length of stay.

Critical Appraisal

The study by Gershengorn et al. was a retrospective analysis funded by Pharmaceutical Research and Manufacturers of America Foundation that studied adults hospitalized with Legionella pneumonia in the United States from 2008-2013. The analysis was conducted on patients discharged from hospitals in the Premiere Perspectives database, the largest drug utilization database in the United States.[1] There are no double-blind, randomized trials comparing azithromycin and quinolones for Legionella pneumonia; therefore, this retrospective analysis was determined to provide the best available evidence for guiding clinical decisions. The OCEBM 2011 Levels of Evidence table would classify this study as having level 3 evidence.[12] The SORT tool from American Family Physician qualifies it as having level 2 quality of evidence.[13] It must be kept in mind however, that since this was not a randomized study, there could have been confounding factors that affected which antibiotic patients received. These confounding factors could also affect the patients' outcome, causing an apparent difference between the two treatments.

The authors reduced the possibility of confounding bias by using propensity-based matching to compare patients treated with azithromycin vs. quinolones.[1] The patients were given a propensity score that used demographic, comorbidity, severity of illness, and hospital data as independent variables. This propensity score is a measure that reflects the propensity for each patient, based on other characteristics, to receive a quinolone vs. azithromycin. Using this method, the authors could compare patients who received a quinolone to patients who received azithromycin but who had a similar propensity or probability of receiving a quinolone. Taking severity of illness into account for the propensity score, and evaluating a second cohort of the most severely ill patients (ICU admission, mechanical ventilation requirements, and predicted probability of hospital mortality in the top quartile for all patients) reduced the possibility of indication bias.

The quinolone and azithromycin groups in this study were similar, with small differences in sex, hospital discharge year, and predicted probability of hospital mortality.[1] There was no clinical difference in hospital mortality between quinolone and azithromycin groups. Propensity matching between the quinolone and azithromycin groups created 813 pairs that were not

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different on any patient or hospital variables. The patient variables included comorbid conditions, illness severity, other forms of management, and length of antibiotic treatment. Hospital variables included size, region, whether the hospital was academic, and whether it was in an urban or rural location.[1] The fact that the study accounted for many important variables with no significant differences between the groups is reassuring and suggests that the cohorts were randomized, and confounding bias is unlikely.

Another possible concern with the study is that it did not include method of diagnosis of Legionella pneumonia among inclusion criteria or relevant patient characteristics when analyzing the study population. Patients were included in the study if they received a diagnosis of Legionella pneumonia, determined by ICD-9 codes. While many cases are diagnosed by Legionella urine antigen, and this method is specific for diagnosis, the study did not analyze or include this information for the study population. Different methods of diagnosis, while unlikely to vary significantly among the study population, could still be a relevant or confounding factor if it was not included in the propensity matching.

The primary outcome in this study was hospital mortality.[1] Secondary outcomes of hospital length of stay, Clostridium difficile colitis, total hospital cost, and discharge destination were also evaluated. All outcomes, primary and secondary, were compared between the quinolone group and the azithromycin group using the chi-squared test and t-test. There were no clinically significant differences in mortality between the quinolone and azithromycin groups both before and after propensity matching. There were also no differences in any of the secondary outcomes apart from a small difference in discharge destination, with a slightly larger percentage of patients from the quinolone group being discharged to skilled nursing or long-term acute care facilities.

Clinical Application

A clinical decision was made, based on both patient preference and the evidence provided by the appraised study, to switch the patient's antibiotic back to azithromycin from moxifloxacin. In hindsight, the recommendation by the infectious diseases team to make the initial change to moxifloxacin caused side effects without added benefit. An important patient factor that affects the external validity of the appraised study and its applicability is the fact that the patient in question had HIV. Azithromycin and quinolones must be studied among an immunocompromised patient population to understand which treatment, if any, provides more benefit for these patients. In our case, the patient remained clinically stable, her chest pain and cough improved, and she was discharged after three days with instructions to finish the remainder of a ten-day course of azithromycin.

The lessons learned are that:

1. There is no mortality or hospital length of stay benefit to using quinolones over azithromycin for Legionella pneumonia.
2. Reviewing research behind practice guidelines and its applicability to clinical situations is a valuable skill for decision-making regarding patient care.
3. Considering patient preferences as part of clinical decisions develops trust and improves relationships between patients and physicians.

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