Published in final edited form as:

Evid Based Med. 2014 December ; 19(6): 226–227. doi:10.1136/ebmed-2014-110061.

Azithromycin for treatment of community-acquired pneumonia: Better than the alternatives?

Wayne A. Ray, Ph.D.

Vanderbilt University School of Medicine: Department of Health Policy (WAR), Village at
Vanderbilt, Suite 2600, 1501 21st Ave South, Nashville, TN 37212

Wayne A. Ray: Wayne.Ray@Vanderbilt.edu

Context

For patients admitted to a regular hospital unit, current U.S. guidelines for treatment of community-acquired pneumonia recommend a 5–7 day course of therapy with either a macrolide plus a 2nd/3rd generation cephalosporin or a respiratory fluoroquinolone (levofloxacin/moxifloxacin).¹ The only guidance for choosing between these alternatives is to avoid antibiotics with patient exposure in the past 3 months. In this context, azithromycin has come under increased scrutiny. We² and others³ have reported that active users of azithromycin have a greater risk of death than do comparable users of amoxicillin, particularly cardiovascular death. However, these studies primarily included patients with short courses of therapy for minor infections, such as sinusitis or bronchitis. In contrast, observational studies of patients with community-acquired pneumonia report that macrolide-based therapy is associated with lower 90 day mortality than fluoroquinolone therapy, hypothesized to be due to beneficial immune effects of macrolides. Thus, Mortensen and colleagues⁴ conducted a nation-wide VA study to compare 90 day mortality in patients treated with azithromycin- or fluoroquinolone-based regimens.

Methods

Retrospective cohort study of patients 65 years of age or older with pneumonia treated according to national clinical practice guidelines. Patients treated with azithromycin and levofloxacin were matched according to propensity score. The primary outcomes were total mortality and cardiovascular events within 30 and 90 days of admission.

Findings

The matched cohort included 31,863 patients in each study group. Those receiving azithromycin had a 27% reduction in the odds of 90 day mortality (OR = 0.73 [0.70–0.76]), increased admissions for myocardial infarction (OR = 1.17 [1.08–1.25]), but no significant difference in total cardiac events (OR = 1.01 [0.98–1.05]). These findings were considered “consistent with a net benefit” for azithromycin.

Commentary

Three leading explanations for the striking decrease in 90 day mortality are a true benefit of azithromycin, unknown effects of the other antibiotics, or unmeasured differences between

the study groups favoring azithromycin. The obvious problem with the first is the magnitude/duration of the mortality benefit. How can a 5–7 day course of therapy with a drug lacking a clear benefit with regard to the underlying infection reduce all-cause mortality by 27%? The beneficial immunologic effect hypothesis would be more plausible in the context of long-term macrolide therapy. It also seems unlikely that the findings could be explained by unknown persistent effects of cephalosporins (beneficial) or respiratory fluoroquinolones (harmful).

The major competing explanation is that the azithromycin group, even after propensity score matching, had a better baseline prognosis. It is now widely appreciated that the pronounced apparent beneficial effects of statins, vaccines, and adherence to therapy—noted for multiple outcomes—are due to these factors being markers for either better prognosis or increased likelihood of receiving better medical care. For the VA study, there was some evidence to support channeling of more favorable prognosis patients to azithromycin. Prior to the matching, these patients had modestly better risk factor profiles for such key indicators as nursing home residence, ICU admission, dementia, and history of malignancy. It is possible that clinicians may favor a single drug regimen for more complex patients. This may explain the reduced protective effect for ICU patients, for whom addition of a cephalosporin to the fluoroquinolone regimen is recommended.¹ Nevertheless, unlike statins, vaccines, and adherence, there is no presently obvious “smoking gun”. Further research on the factors that distinguish patients prescribed azithromycin versus a respiratory fluoroquinolone would be useful.

What role should the cardiac effects of azithromycin play in determining therapy for community-acquired pneumonia? The electrophysiologic properties of levofloxacin and moxifloxacin suggest they would have equal or greater pro-arrhythmogenicity than azithromycin.⁵ Indeed, moxifloxacin so reliably prolongs the QT interval that it is a frequent positive control in the thorough QT studies mandated by the FDA.⁶ Cohort studies have found that current levofloxacin use increases risk of death,^{2,4} perhaps to a greater extent than azithromycin.³ Thus, absent equally effective antimicrobials with fewer cardiac effects, the “key to appropriate therapy” should be antimicrobial coverage of the responsible pathogen.¹

Should the findings of Mortensen and colleagues alter clinical practice? I believe not, given the uncertainty as to whether or not the VA study findings reflect a true clinical benefit. Azithromycin (or other macrolides) ultimately may be favored, but this should await a more compelling mechanistic basis for a beneficial effect, better elucidation of the adverse effects of alternative regimens, or the findings of adequately powered clinical trials. In this regard, at least one large randomized clinical trial of therapy for community-acquired pneumonia is underway in Europe.⁷ The findings will be of intense clinical interest.

Acknowledgments

Supported by a grant from the NHLBI (# HL081707)

References

1. Wunderink RG, Waterer GW. Community-acquired pneumonia. *N Engl J Med*. 2014; 370:543–551. [PubMed: 24499212]
2. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *N Engl J Med*. 2012; 366:1881–1890. [PubMed: 22591294]
3. Rao GA, Mann JR, Shoaibi A, et al. Azithromycin and levofloxacin use and increased risk of cardiac arrhythmia and death. *Ann Fam Med*. 2014; 12:121–127. [PubMed: 24615307]
4. Mortensen EM, Halm EA, Pugh MJ, et al. Association of azithromycin with mortality and cardiovascular events among older patients hospitalized with pneumonia. *JAMA*. 2014; 311:2199–2208. [PubMed: 24893087]
5. Owens RC, Nolin TD. Antimicrobial-associated QT interval prolongation: Pointes of interest. *Clin Infect Dis*. 2006; 43:1603–1611. [PubMed: 17109296]
6. FDA. FDA drug safety communication: Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. Safety Announcement. 2011
7. van Werkhoven CH, Postma DF, Oosterheert JJ, Bonten MJM. Antibiotic treatment of moderate-severe community-acquired pneumonia: design and rationale of a multicentre cluster-randomised cross-over trial. *Netherlands Journal of Medicine*. 2014; 72:170–178. [PubMed: 24846935]