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Q/ Does prophylactic azithromycin reduce the number of COPD exacerbations or hospitalizations?

EVIDENCE-BASED ANSWER

A/ YES FOR EXACERBATIONS, NO FOR HOSPITALIZATIONS. Prophylactic azithromycin reduces the number of exacerbations by about 25%. It also extends the time between exacerbations by approximately 90 days for patients with moderate-to-severe chronic obstructive pulmonary disease (COPD). Azithromycin benefits patients who are >65 years, patients with Global Initiative for Obstructive Lung Dis-

ease (GOLD) stage II or III COPD, former smokers, and patients using long-term oxygen; it doesn't benefit patients ≤65 years, patients with GOLD stage IV COPD, current smokers, or patients not using oxygen (strength of recommendation [SOR]: **B**, randomized controlled trials [RCTs]).

Prophylactic azithromycin doesn't reduce hospitalizations overall (SOR: **B**, single small RCT).

Evidence summary

A randomized, placebo-controlled trial including 1142 patients with COPD (forced expiratory volume in one second [FEV₁] <70%, postbronchodilator FEV₁ <80%) found that daily azithromycin 250 mg reduced acute exacerbations more than placebo over one year.¹ Researchers recruited patients who were using supplemental oxygen, had required glucocorticoids, or had been hospitalized for an acute exacerbation in the last year. Patients with asthma, resting heart rate >100 beats/min, prolonged QTc interval (or on prolonging medications), or hearing impairment were excluded.

Azithromycin increased the median time to first exacerbation (defined as increase or new onset of cough, sputum, wheeze, and chest tightness for 3 days requiring antibiotics or systemic steroids) compared with the placebo group (266 days vs 174 days; $P<.001$) and reduced the risk of an acute exacerbation per patient year (hazard ratio [HR]=0.73; 95% confidence [CI], 0.63-0.84). It also reduced

the rate of acute exacerbations per patient year (1.83 vs 1.43; $P=.01$; rate ratio=0.83; 95% CI, 0.72-0.95). The number needed to treat to prevent one exacerbation was 2.86.

No differences in death from any cause (3% vs 4%; $P=.87$), death from respiratory cause (2% vs 1%; $P=.48$), or death from cardiovascular cause (0.2% vs 0.2%; $P=1.0$) were found between azithromycin and placebo. Nor did rates of hospitalizations for acute exacerbations differ.

The groups also showed no significant difference in serious adverse events leading to discontinuation of medication. Notably, more patients in the azithromycin group had audiogram-confirmed hearing loss (25% vs 20%; $P=.04$), although the authors state that their criteria for hearing loss may have been too stringent because hearing improved on repeat testing whether or not the study drug was discontinued. In addition, more patients in the placebo group developed nasopharyngeal colonization with methicillin-resistant *Staphylococcus aureus* (31% vs 12%; $P<.001$).

Older ex-smokers on long-term O₂ benefit most from the antibiotic

A retrospective subgroup analysis of the RCT identified patients who benefited most from daily azithromycin therapy.² Compared with placebo, azithromycin decreased the time to first exacerbation in patients >65 years (542 patients; HR=0.59; 95% CI, 0.47-0.74), but not patients ≤65 years (571 patients; HR=0.84; 95% CI, 0.68-1.04).

The azithromycin group also demonstrated decreased time to first exacerbation in ex-smokers (867 patients; HR=0.65; 95% CI, 0.55-0.77) and patients on long-term oxygen (659 patients; HR=0.66; 95% CI, 0.55-0.80) but not current smokers (246 patients; HR=0.99; 95% CI, 0.71-1.38) or patients not using long-term oxygen (454 patients; HR=0.80; 95% CI, 0.62-1.03).

Azithromycin administration decreased exacerbations in patients with GOLD stages II (292 patients; HR=0.55; 95% CI, 0.40-0.75) and III (451 patients; HR=0.71; 95% CI, 0.56-0.90), but not stage IV (370 patients; HR=0.84; 95% CI, 0.65-1.08). The significance of the results is limited because the study was not originally powered for this level of subgroup analysis.

Smaller study shows similar results

A smaller RCT of 92 patients that evaluated exacerbation rates with azithromycin and placebo recruited patients with at least 3 acute COPD exacerbations in the previous year.³

Compared with placebo, oral azithromycin 500 mg 3 times a week (Monday, Wednesday, and Friday) increased the time between

exacerbations over a 12-month period (59 days vs 130 days; $P=.001$). It also reduced the exacerbation rate per person per year (1.94 vs 3.22; risk ratio=0.60; 95% CI, 0.43-0.84) but didn't change the hospitalization rate (odds ratio=1.34; 95% CI, 0.67-2.7).

No difference in serious adverse events was found between the azithromycin and placebo groups (3 patients vs 5 patients; $P=NS$), but an increase in diarrhea (9 patients vs 1 patient; $P=.015$) was noted.

Recommendations

An evidence-based guideline by the American College of Chest Physicians and Canadian Thoracic Society recommends long-term macrolide therapy to prevent acute exacerbations in patients >40 years with moderate or severe COPD and a history of ≥1 moderate or severe exacerbation in the previous year despite maximized inhaler therapy (Grade 2A, weak recommendation, high-quality evidence).⁴ The guideline also states that the duration and optimal dosages are unknown. **JFP**

References

1. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med*. 2011;365:689-698.
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3. Pomares X, Montón C, Espasa M, et al. Long-term azithromycin therapy in patients with severe COPD and repeated exacerbations. *Int J Chron Obstruct Pulmon Dis*. 2011;6:449-456.
4. Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. *Chest*. 2015;147: 894-942.

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