

1-MINUTE CONSULT

ABDULRAZAK ALCHAKAKI, MD

Division of Pulmonary, Critical Care, and Sleep Medicine, Wayne State University School of Medicine, Detroit, MI

CASSONDR A CRAMER

Division of Pulmonary, Critical Care and Sleep Medicine, Wayne State University School of Medicine, Detroit, MI

ALLIE PATTERSON

Division of Pulmonary, Critical Care, and Sleep Medicine, Wayne State University School of Medicine, Detroit, MI

AYMAN O. SOUBANI

Division of Pulmonary, Critical Care, and Sleep Medicine, Wayne State University School of Medicine, Detroit, MI



BRIEF ANSWERS
TO SPECIFIC
CLINICAL
QUESTIONS

Q: Which patients with respiratory disease need long-term azithromycin?

A: Azithromycin is prescribed for a variety of acute respiratory and nonrespiratory infections. However, it is also used in several chronic respiratory diseases.

MECHANISM OF ACTION

Macrolide antibiotics like azithromycin inhibit bacterial growth and replication by interrupting protein synthesis. But azithromycin also has immunomodulatory properties.¹

In the acute phase of inflammation, azithromycin exerts an initial neutrophil degranulation effect and enhances the oxidative response that is primed by particulate stimulus, which could facilitate its antibacterial effects. In the late phase, it down-regulates the oxidative burst and increases apoptosis of neutrophils to promote healing without compromising immunity. Azithromycin also attenuates airway mucus hypersecretion, improves ciliary function, and promotes pulmonary epithelial cell healing.^{2,3}

Collectively, these effects make the drug effective in many chronic inflammatory lung conditions (Table 1).

CYSTIC FIBROSIS

Cystic fibrosis is a genetic disease affecting many organs, but its effect on the upper and lower airways has the greatest impact on quality of life and survival. Impaired mucociliary clearance and repeated respiratory infections contribute to chronic inflammation and a progressive decline in lung function.^{4,5}

A 2012 Cochrane review of 5 studies in 549 patients found that, compared with those taking placebo, patients taking azithromycin

250–500 mg 3 times a week had improvement in forced expiratory volume in 1 second (FEV₁). The mean difference at 6 months was 3.97% (95% confidence interval [CI] 1.74–6.19). Patients on azithromycin were free from pulmonary exacerbation approximately twice as long as patients on placebo (odds ratio 1.96, 95% CI 1.15–3.33).^{6,7}

The Cystic Fibrosis Foundation recommends long-term azithromycin therapy to improve lung function and reduce exacerbations in patients age 6 or older who have persistent *Pseudomonas aeruginosa* airway cultures (level of evidence: fair).⁸

DIFFUSE PANBRONCHIOLITIS

Diffuse panbronchiolitis, or diffuse chronic inflammatory bronchiolitis and sinusitis, is seen mainly in patients of Asian descent.⁹ In the past, the mortality rate was greater than 90%, but between 1970 and 1979 the 10-year survival rate increased by more than 40% with chronic macrolide therapy, ie, with erythromycin.^{10,11}

Later retrospective studies of azithromycin 500 mg 3 times a week showed results comparable to those with erythromycin, with improvement in symptoms, lung function, arterial partial pressure of oxygen, and radiologic findings, as well as fewer adverse effects.¹² These benefits justify the current recommendation for azithromycin as the mainstay of therapy in diffuse panbronchiolitis.

BRONCHIOLITIS OBLITERANS SYNDROME

Bronchiolitis obliterans syndrome is an airflow limitation that arises without infection or imaging evidence of bronchiolitis in patients who received allogeneic hematopoietic stem

Long-term use should be individualized, weighing benefits against risks and monitoring for adverse effects

TABLE 1

Indications for azithromycin in respiratory conditions**Antibacterial indications**

Pharyngitis, tonsillitis (with penicillin allergy)
 Acute exacerbation of chronic bronchitis
 Community-acquired pneumonia
 Prevention of *Mycobacterium avium* complex (and part of treatment regimen)

Immunomodulatory indications

Cystic fibrosis
 Diffuse panbronchiolitis
 Posttransplant bronchiolitis obliterans syndrome
 Non-cystic fibrosis bronchiectasis
 Chronic obstructive pulmonary disease

cell or lung transplant. It occurs in 50% of lung transplant recipients as a form of chronic graft rejection and in 6% to 20% of allogeneic stem cell transplant recipients as a manifestation of chronic graft-vs-host disease.^{13,14}

Azithromycin has been used in its management. A meta-analysis of lung transplant recipients found a significant improvement in the survival rate and overall lung function after an average of 7 months of treatment with azithromycin, with a mean increase in FEV₁ of 8.8% (95% CI 5.1–12.47, $P < .001$).¹⁴ The evidence currently supports long-term azithromycin 250 mg 3 times a week after lung transplant to reduce any decline in lung function and to lower the mortality rate.^{14,15}

In allogeneic stem cell transplant recipients, the evidence for long-term azithromycin treatment is sparse. A recent prospective multicenter study evaluated the effect of an azithromycin-based regimen (fluticasone, azithromycin, and montelukast, plus a steroid pulse) in stem cell recipients with bronchiolitis obliterans syndrome during the first 3 months after diagnosis. In the treated group, 6% had a drop in FEV₁ of more than 10% at 3-month follow-up compared with 40% of historical controls (95% CI 1%–19%, $P < .001$). Also, treatment resulted in a 50% re-

duction in the dose of systemic steroids and a substantial improvement in functional status.¹⁶

Given the limited options in the management of these patients and until further studies are available, azithromycin 3 times weekly is suggested.

■ NON-CYSTIC FIBROSIS BRONCHIECTASIS

Non-cystic fibrosis bronchiectasis is a chronic inflammatory lung condition characterized by irreversible dilation of the bronchi and bronchioles due to a variety of causes including recurrent or old infection, immunodeficiency, autoimmune conditions, and connective tissue disease; it can also be idiopathic.¹⁷

Altenburg et al,¹⁸ in a randomized, double-blind, placebo-controlled trial, found that azithromycin 250 mg 3 times a week for 12 months reduced the number of exacerbations from a median number of 2 per patient with placebo to 0 per patient with azithromycin ($P < .001$). At 3 months, the FEV₁ as a percent of predicted had increased by 1.03% in the azithromycin group and decreased by 0.10% in the placebo group ($P = .047$). The number needed to treat with azithromycin to maintain clinical stability was 3.0.

Wong et al¹⁹ randomized patients to receive azithromycin 500 mg 3 times a week or placebo for 6 months. The rate of exacerbations was 0.59 per patient in the azithromycin group and 1.57 per patient in the placebo group ($P < .0001$). The FEV₁ remained unchanged from baseline in the azithromycin group while decreasing in the placebo group, but the difference was not significant.

■ EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are a major cause of death, poor quality of life, and healthcare expenditures.²⁰ Prevention is therefore of the utmost importance.

Several studies have shown that azithromycin prophylaxis can reduce acute exacerbations of COPD. A recent meta-analysis showed that long-term macrolide prophylaxis significantly reduced exacerbations compared with rates in controls (risk ratio = 0.70,

Studies have shown that azithromycin prophylaxis can reduce acute exacerbations of COPD

95% CI 0.56–0.87, $P < .01$) and increased the median time to first COPD exacerbation by more than 90 days ($P < .01$).²¹ Long-term azithromycin therapy may be considered in selected patients who have frequent exacerbations despite optimal maintenance inhaler therapy.

■ PROPHYLAXIS IN IMMUNODEFICIENCY

Disseminated *Mycobacterium avium* complex (MAC) is an opportunistic infection most commonly occurring in patients with acquired immunodeficiency syndrome with CD4 counts below 50 cells/ μL .^{22,23}

In a double-blinded, randomized trial, patients who received azithromycin had a 47% reduction in the incidence of MAC infection.

Given the long half-life of azithromycin, it is effective with once-weekly dosing of 1,200 mg.²³ Ideally, patients are placed on a prophylactic agent for disseminated MAC infection until the CD4 count reaches 100 cells/ μL and remains at or above this level for 3 consecutive months.²⁴

■ ADVERSE EFFECTS AND PRECAUTIONS

Long-term azithromycin therapy may produce bacterial resistance; the risk has been estimat-

ed at 2.7 times greater in patients who are on long-term azithromycin treatment.²⁵ Also, patients at risk for MAC infection, such as those with cystic fibrosis, should be screened for it before starting treatment in order to prevent resistance to azithromycin.

The US Food and Drug Administration warns that azithromycin can lead to a prolonged corrected QT interval and potential fatal arrhythmias such as torsades de pointes. Major reviews have largely agreed that arrhythmias are more pronounced in patients with a coexisting cardiac risk factor such as existing QT-interval prolongation, low blood levels of potassium or magnesium, a slower than normal heart rate, or arrhythmias, or who are on class IA and III antiarrhythmic drugs.^{26–28}

Other potential adverse effects of long-term azithromycin treatment are gastrointestinal symptoms and hearing impairment.^{29,30} A review of potential drug interactions is advised when patients are placed on long-term azithromycin therapy.

Although azithromycin is generally well tolerated, long-term treatment should be individualized and the benefits weighed against the risks. Patients should be monitored during treatment for any of the above adverse effects. ■

■ REFERENCES

- Bailey S, Pocardalo JJ, Fay M, Gougerot-Pocidal MA. Differential modulation of cytokine production by macrolides: interleukin-6 production is increased by spiramycin and erythromycin. *Antimicrob Agents Chemother* 1991; 35:2016–2019.
- Kanoh S, Rubin BK. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. *Clin Microbiol Rev* 2010; 23:590–615.
- Culić O, Eraković V, Cepelak I, et al. Azithromycin modulates neutrophil function and circulating inflammatory mediators in healthy human subjects. *Eur J Pharmacol* 2002; 450:277–289.
- Cohen-Cyberknoh M, Kerem E, Ferkol T, Elizur A. Airway inflammation in cystic fibrosis: molecular mechanisms and clinical implications. *Thorax* 2013; 68:1157–1162.
- Sagel SD, Wagner BD, Anthony MM, Emmett P, Zemanick ET. Sputum biomarkers of inflammation and lung function decline in children with cystic fibrosis. *Am J Respir Crit Care Med* 2012; 186:857–865.
- Saiman L, Anstead M, Mayer-Hamblett N, et al; AZ0004 Azithromycin Study Group. Effect of azithromycin on pulmonary function in patients with cystic fibrosis uninfected with *Pseudomonas aeruginosa*: a randomized controlled trial. *JAMA* 2010; 303:1707–1715.
- Southern KW, Barker PM, Solis-Moya A, Patel L. Macrolide antibiotics for cystic fibrosis. *Cochrane Database Syst Rev* 2012; 11:CD002203.
- Flume PA, O'Sullivan BP, Robinson KA, et al; Cystic Fibrosis Foundation, Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med* 2007; 176:957–969.
- Yanagihara K, Kadoto J, Kohno S. Diffuse panbronchiolitis—pathophysiology and treatment mechanisms. *Int J Antimicrob Agents* 2001; 18(suppl 1):S83–S87.
- Kudoh S, Azuma A, Yamamoto M, Izumi T, Ando M. Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. *Am J Respir Crit Care Med* 1998; 157:1829–1832.
- Schultz MJ. Macrolide activities beyond their antimicrobial effects: macrolides in diffuse panbronchiolitis and cystic fibrosis. *J Antimicrob Chemother* 2004; 54:21–28.
- Hui D, Yan F, Chen RH. The effects of azithromycin on patients with diffuse panbronchiolitis: a retrospective study of 29 cases. *J Thorac Dis* 2013; 5:613–617.
- Khalid M, Al Saghir A, Saleemi S, et al. Azithromycin in bronchiolitis obliterans complicating bone marrow transplantation: a preliminary study. *Eur Respir J* 2005; 25:490–493.
- Kingah PL, Muma G, Soubani A. Azithromycin improves lung function in patients with post-lung transplant bronchiolitis obliterans syndrome: a meta-analysis. *Clin Transplant* 2014; 28:906–910.
- Corris PA, Ryan VA, Small T, et al. A randomised controlled trial of azithromycin therapy in bronchiolitis obliterans syndrome (BOS) post lung transplantation. *Thorax* 2015; 70:442–450.
- Williams KM, Cheng GS, Pusic I, et al. Fluticasone, azithromycin, and montelukast treatment for new-onset bronchiolitis obliterans syndrome after hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2016; 22:710–716.
- Haworth CS, Bilton D, Elborn JS. Long-term macrolide maintenance therapy in non-CF bronchiectasis: evidence and questions. *Respir Med* 2014; 108:1397–1408.

AZITHROMYCIN

18. **Altenburg J, de Graaff CS, Stienstra Y, et al.** Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. *JAMA* 2013; 309:1251–1259.
19. **Wong C, Jayaram L, Karalus N, et al.** Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2012; 380:660–667.
20. **Suissa S, Dell’Aniello S, Ernst P.** Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax* 2012; 67:957–963.
21. **Ni W, Shao X, Cai X, et al.** Prophylactic use of macrolide antibiotics for the prevention of chronic obstructive pulmonary disease exacerbation: a meta-analysis. *PLoS One* 2015; 10:e0121257.
22. **Griffith DE, Aksamit T, Brown-Elliott BA, et al; ATS Mycobacterial Diseases Subcommittee; American Thoracic Society; Infectious Disease Society of America.** An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007; 175:367–416.
23. **Havliir DV, Dubé MP, Sattler FR, et al.** Prophylaxis against disseminated *Mycobacterium avium* complex with weekly azithromycin, daily rifabutin, or both. California Collaborative Treatment Group. *N Engl J Med* 1996; 335:392–398.
24. **Uthman MM, Uthman OA, Yahaya I.** Interventions for the prevention of *Mycobacterium avium* complex in adults and children with HIV. *Cochrane Database Syst Rev* 2013; 4:CD007191.
25. **Li H, Liu DH, Chen LL, et al.** Meta-analysis of the adverse effects of long-term azithromycin use in patients with chronic lung diseases. *Antimicrob Agents Chemother* 2014; 58:511–517.
26. **Svanström H, Pasternak B, Hviid A.** Use of azithromycin and death from cardiovascular causes. *N Engl J Med* 2013; 368:1704–1712.
27. **Albert RK, Schuller JL; COPD Clinical Research Network.** Macrolide antibiotics and the risk of cardiac arrhythmias. *Am J Respir Crit Care Med* 2014; 189:1173–1180.
28. **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.
29. **Albert RK, Connett J, Bailey WC, et al; COPD Clinical Research Network.** Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011; 365:689–698.
30. **Broad J, Sanger GJ.** The antibiotic azithromycin is a motilin receptor agonist in human stomach: comparison with erythromycin. *Br J Pharmacol* 2013; 168:1859–1867.

ADDRESS: Abdulrazak Alchakaki, MD, Division of Pulmonary, Critical Care, and Sleep Medicine, Wayne State University School of Medicine, 3990 John R, 3 Hudson, Detroit, MI 48201; aalchaka@med.wayne.edu

Join Our Team

Growth. Advancement. Opportunity.

These are just a few reasons to join our team of physicians and advance practice providers at Cleveland Clinic in Ohio, Florida, Nevada, Abu Dhabi and London. As a physician-led organization, we base our culture on collaboration and Patients First. Because we push the boundaries of performance, we offer competitive compensation and benefits that equal or surpass our peer organizations.

To learn more and view our physician staff and advanced practice listings, please visit jobs.clevelandclinic.org.

Cleveland Clinic is pleased to be an equal employment/affirmative action employer: Women/Minorities/Veterans/Individuals with Disabilities. Smoke/drug free environment.



Cleveland Clinic

Every life deserves world class care.