



# Should you consider antibiotics for exacerbations of mild COPD?

Yes. Guidelines recommend antibiotics for exacerbations in patients with moderate to severe COPD, and evidence shows they may be effective for those with mild COPD.

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## PRACTICE CHANGER

Consider antibiotics for patients with exacerbations of mild to moderate chronic obstructive pulmonary disease (COPD).<sup>1</sup>

- have 2 of these 3 symptoms if increased sputum purulence is one of the symptoms; or
- require mechanical ventilation.<sup>2</sup>

## STRENGTH OF RECOMMENDATION

**B:** Based on a single well-done multicenter randomized controlled trial (RCT) with quality evidence.

Llor C, Moragas A, Hernández S, et al. Efficacy of antibiotic therapy for acute exacerbations of mild to moderate chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2012;186:716-723.

According to the GOLD guidelines, the choice of antibiotic should be based on local antibiograms; common options include amoxicillin, amoxicillin/clavulanate, azithromycin, and doxycycline.<sup>2</sup> Although the GOLD guidelines cover use of antibiotics for COPD exacerbations, this recommendation is based on analyses of studies that focused on patients with moderate or severe COPD.<sup>2</sup> There has been little research on using antibiotics for exacerbations of mild COPD.

## ILLUSTRATIVE CASE

A 45-year-old man with a history of mild COPD seeks treatment for worsening dyspnea and increased (nonpurulent) sputum production. He denies fever or chills. On exam, he has coarse breath sounds and scattered wheezes. Should you add antibiotics to his treatment?

## STUDY SUMMARY

### Using antibiotics often resolves symptoms

Llor et al<sup>1</sup> conducted a multicenter, double-blind placebo-controlled RCT to examine the effectiveness of antibiotic treatment for COPD exacerbations. Participants (ages ≥40 years) had mild to moderate COPD, defined as ≥10 pack-years of smoking, a forced expiratory volume in 1 second (FEV<sub>1</sub>) >50%, and a FEV<sub>1</sub>-to-forced vital capacity ratio <0.7. An exacerbation was defined as at least one of the following: increased dyspnea, increased sputum volume, or sputum purulence. Patients were randomized to receive amoxicillin/clavulanate 500/125 mg or placebo 3 times a day for 8 days. The primary

**C**OPD exacerbations—a worsening of symptoms beyond day-to-day variations that leads to a medication change—are part of the disease course and can accelerate lung function decline, decrease quality of life, and, when severe, increase mortality.<sup>2</sup> Infections cause an estimated 50% to 70% of COPD exacerbations.<sup>2-4</sup>

Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend using antibiotics to treat exacerbations in patients with moderate or severe COPD who:

- have increased dyspnea, sputum volume, and sputum purulence;

➤ **By Day 11, symptoms resolved in 74.1% of patients in the antibiotic group, compared with 59.9% in the placebo group.**

endpoints were clinical cure (resolution of symptoms) and clinical success (resolution or improvement of symptoms) at Days 9 to 11 as determined by physician assessment. Secondary measures included cure and clinical success at Day 20 and time until next exacerbation. Patients were monitored for one year after the exacerbation.

There were 162 patients in the antibiotic group and 156 in the placebo group; the 2 groups were demographically similar. In each group, 4 patients withdrew consent and were removed from analysis. By the 9- to 11-day follow-up visit, 74.1% of patients in the antibiotic group had clinical cure, compared with 59.9% in the placebo group ( $P=.016$ ; number needed to treat [NNT]=7). Clinical success also was significantly greater with antibiotics compared with placebo (90.5% vs 80.9%;  $P=.022$ ).

The clinical cure rate at Day 20 also was significantly greater in patients on antibiotics compared with placebo (81.6% vs 67.8%;  $P=.006$ , NNT=7). During the one-year follow-up, 58% of patients in the antibiotic group and 73.2% of those in the placebo group experienced additional exacerbations. Time to next exacerbation was significantly longer in patients taking antibiotics (233 days vs 160 days;  $P=.015$ ).

**■ Can CRP level help determine who should—and shouldn't—receive antibiotics?** Previous studies have identified biomarkers, including C-reactive protein (CRP), that indicate COPD exacerbation, but have not linked them to clinical course.<sup>5-7</sup> In this study, researchers measured CRP in patients receiving placebo to determine if this biomarker could predict clinical outcomes.

The researchers found that the clinical success rate among patients with a CRP <40 mg/L was 87.6%, while only 34.5% of patients with a CRP >40 mg/L experienced clinical success (sensitivity and specificity for clinical success at this cutoff was 0.655 and 0.876, respectively). This suggests that antibiotics might be appropriate for patients with an exacerbation of mild or moderate COPD who have a CRP >40 mg/L.

A total of 35 adverse events were reported: 23 in patients taking antibiotics and 12 among patients receiving placebo. Only 2 patients discontinued treatment due to adverse events in

antibiotics group. Most of these reactions were mild gastrointestinal problems.

#### WHAT'S NEW

##### Evidence supports antibiotics for mild to moderate COPD

Few placebo-controlled trials have addressed antibiotic use for exacerbations in patients with mild to moderate COPD.<sup>2,8,9</sup> This study demonstrated that compared with placebo, symptom resolution and clinical success is greater with amoxicillin/clavulanate, and that antibiotic treatment also may increase time until next exacerbation.

The study also looked at the relationship of CRP and exacerbations in the placebo group. Higher spontaneous clinical cure rates were noted when the CRP was <40 mg/L.

#### CAVEATS

##### Effects of concomitant medications are unclear

In both the placebo and antibiotic groups, patients were taking other medications (including short- and long-acting beta-agonists, anticholinergics, theophyllines, and oral or inhaled corticosteroids). Roughly the same number of patients in each group took additional medications, but researchers did not conduct a subgroup analysis to see if patients treated with these medications responded differently than those who received antibiotics alone.

GOLD guidelines already suggest antibiotics for exacerbations in patients with moderate COPD.<sup>2</sup> In this study, 89% of patients met criteria for moderate COPD and 11% for mild COPD. Though the percentage of patients who had mild COPD was small, we believe the results of this study warrant consideration of antibiotic use in patients with mild disease.

Local antibiograms may show increased resistance to amoxicillin/clavulanate; this study did not address the use of other antibiotics.

#### CHALLENGES TO IMPLEMENTATION

##### Antibiotic overuse may be a concern

With increased awareness of inappropriate

antibiotic use, physicians might have concerns about antibiotic resistance developing as a result of using antibiotics for exacerbations of mild to moderate COPD. **JFP**

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**Clinical success also was significantly greater with antibiotics compared with placebo.**