



## Antibiotic Guidance for Treatment of Acute Exacerbations of COPD (AECOPD) in Adults

Antibiotics are **not** recommended for all patients with AECOPD as bacterial infection is implicated in less than one-third of AECOPD. Procalcitonin (PCT) may be helpful in determining if antibiotics are necessary or the duration of treatment. All antibiotic dosages listed below are based on normal renal and hepatic function. The typical duration of therapy for AECOPD is 5 days.

**Antibiotics should only be started or continued in patients with signs and symptoms of a bacterial infection that include the following:**

- 1) Increased dyspnea, increased purulence of sputum, and increased volume of sputum OR
- 2) Ventilator support (invasive or non-invasive) for AECOPD

**Patients with a PCT <0.1 ng/mL are unlikely to benefit from antibiotic administration**

- **Mild exacerbation (no respiratory failure<sup>+</sup>, FEV<sub>1</sub> >50% predicted, < 3 exacerbations/year)**
  - 1<sup>st</sup> line: Doxycycline 100 mg PO BID OR Cefuroxime 500 mg PO BID
  - 2<sup>nd</sup> line: Azithromycin 500 mg PO daily\*
- **Moderate exacerbation (non-life-threatening respiratory failure<sup>+</sup>, FEV<sub>1</sub> 36-50%, ≥ 3 exacerbations/year, ≥65 years of age)**
  - 1<sup>st</sup> line: Amoxicillin-clavulanate 875-125 mg PO BID OR Doxycycline 100 mg PO BID
  - 2<sup>nd</sup> line: Azithromycin 500 mg PO daily\*
- **Severe exacerbation (life-threatening respiratory failure<sup>+</sup>, baseline FEV<sub>1</sub> ≤35%) OR Requires ventilator support:**
  - No risk factors for *Pseudomonas aeruginosa*:
    - Ceftriaxone 1 gram IV every 24 hours (>80 kg: Ceftriaxone 2 grams IV every 24 hours)
    - Severe beta-lactam allergy: Levofloxacin 750 mg PO or IV every 24 hours\*\*
  - Risk factors for *Pseudomonas aeruginosa* (see Table 1):
    - 1<sup>st</sup> line: Cefepime 1 gram IV every 6 hours
    - 2<sup>nd</sup> line: Piperacillin-tazobactam 4.5 grams IV every 8 hours
    - Severe beta-lactam allergy: Aztreonam 2 grams IV every 8 hours + levofloxacin 750 mg po or IV every 24 hours\*\*

+ Respiratory status adapted from the 2018 GOLD guidelines. See Table 1. For patients with re-admission within 30 days or recurrent AECOPD, consider expert consultation with a pulmonologist.

\* Consider ECG prior to initiating, especially if other QTc-prolonging medications are present. Alternate therapy may need to be considered in patients at high risk of cardiovascular events.

\*\* **As of July 2016**, the FDA no longer recommends fluoroquinolones for the treatment of acute exacerbations of bronchitis. This therapy should be reserved for severe beta-lactam allergy where no other treatment options are available. Current labeling includes a black box warning for CNS effects, tendonitis or tendon rupture, and peripheral neuropathy that may be irreversible. Consider ECG prior to initiating, especially in patients with other QTc-prolonging medications.

## Chronic Obstructive Pulmonary Disease Pathway

### PURPOSE:

To provide a framework for the initial evaluation and management of patients admitted with acute exacerbations of chronic obstructive pulmonary disease (COPD) based on recent literature and guidelines. Appropriate management of these exacerbations can have a significant impact on the patient's morbidity and mortality; therefore, it is important that evidence-based regimens are utilized in these patients. Antibiotics are often used in acute exacerbations of COPD (AECOPD) as bacteria are commonly implicated in these patients; however, exacerbations may be caused by viruses and other environmental factors. This document will provide the clinician with guidance to assist with diagnosis and management of AECOPD. COPD order sets are available within One Chart and contain much of the information below. These order sets should be utilized as they provide a convenient way to provide evidence-based care to patients at Nebraska Medicine.

### DEFINITION<sup>1</sup>:

**Chronic Obstructive Pulmonary Disease (COPD)** is a progressive respiratory disease characterized by inflammation and structural changes leading to decreased airflow. The most common symptoms of COPD include chronic cough, dyspnea, and sputum production. The disease includes emphysema and obstructive bronchiolitis. Chronic bronchitis may be present in patients with COPD, but it is considered to be a separate disease state. COPD affects millions of patients in the United States and exacerbations account for a significant proportion of healthcare expenditures each year.

**Acute Exacerbation of COPD (AECOPD)** is defined as a sudden worsening of the patient's symptoms requiring medical intervention. AECOPD can have a significant impact on the patient's prognosis and mortality. Exacerbations requiring hospitalization have a risk of mortality of approximately 10%. If the patient is critically ill and requires support with a ventilator, mortality can be as high as 40% in the year after discharge. While bacteria and viruses are commonly implicated as causes of AECOPD, up to one-third of exacerbations may be caused by an unknown source.

### DIAGNOSIS<sup>1</sup>:

Currently, diagnosis is made primarily based on the patient's symptoms. The GOLD guidelines focus on the "cardinal symptoms", or Anthonisen criteria, which include an increase in dyspnea, sputum purulence and/or sputum volume. Other tests such as cardiac monitoring, a chest X-ray, laboratory data, pulse oximetry and/or sputum sampling may be useful in determining the severity of the exacerbation and differentiating AECOPD from other respiratory conditions such as pneumonia. Spirometry is not recommended in patients with an AECOPD.

Bacterial exacerbations may be caused by colonization or infection of the respiratory tract with new strains of bacteria. As patients with COPD are likely to have bacterial colonization, sputum cultures can be difficult to interpret unless previous culture data is available for comparison. Therefore, sputum cultures are not appropriate in most patients and are not routinely recommended. Patients who have frequent exacerbations or who require mechanical ventilation may benefit from sputum culture to evaluate for gram negative pathogens which are more common in this population. A respiratory viral panel may be considered for patients that present with symptoms of a viral illnesses (especially during influenza season) or in those that are critically ill. For most patients, treatment of viral illness is directed at symptoms and the respiratory viral panel will not significantly change management for the patient unless it is useful in withholding antibiotics. Procalcitonin (addressed below) is not useful in the diagnosis of AECOPD but may be helpful in determining when to use antibiotics.

## **MANAGEMENT OF AECOPD:**

### **PROCALCITONIN:**

While antibiotics have been found to provide some benefit in AECOPD, several studies can provide clinicians with guidance as to which patients are most likely to benefit from antibiotic therapy. Procalcitonin (PCT) has been shown to be useful in guiding antimicrobial therapy in patients with lower respiratory tract infections, including AECOPD.

A number of randomized trials have found that patients with low (<0.25 ng/mL) PCT levels, and in particular those whose levels are <0.1 ng/mL, do not benefit from antibiotics. For example, in a recent randomized trial by Wang et al., patients with AECOPD and a PCT level <0.1 ng/mL did not benefit from antibiotic therapy. Patients who had not received antibiotics achieved a clinical success rate on day 10 of 95.8% versus 93.7% in patients who were placed on broad-spectrum antibiotic therapy with no significant difference in the antibiotic use after discharge, rate of intubation, length of stay, mortality or re-hospitalization between groups over the next 30 days.<sup>2</sup> These results have been confirmed in a meta-analysis with PCT-guided therapy decreasing antibiotic use by 74% without any increase in mortality, clinical failure, readmission, or recurrent exacerbation.<sup>3,4</sup>

In AECOPD, PCT can help clinicians determine the likelihood of a bacterial versus viral infection, severity of illness, or appropriate length of antibiotic therapy. Based on the available literature, antibiotics do not appear to provide benefit in patients with AECOPD and a PCT <0.1 ng/mL. Values between 0.1 and 0.25 ng/mL suggest antibiotics are unlikely to be of benefit, but decisions regarding antibiotic administration should be individualized based on clinical factors such as the severity of illness. Further information on PCT use in respiratory tract infections is available on the ASP website.

### **ANTIBIOTICS:**

Although at least half of patients that present with AECOPD have sputum cultures positive for bacteria, it can be difficult to determine whether these cultures represent colonization or true pathogens.<sup>1,5</sup> While some patients with AECOPD benefit from antibiotics, it is important to note that there are other causes of exacerbations with viruses identified in up to 60% of exacerbations. Therefore, not all patients who present with AECOPD should receive antibiotics.

The GOLD guidelines recommend that antibiotics be initiated in patients with AECOPD who meet the following criteria: 1) critically ill and/or requiring mechanical ventilation or 2) present with the three “cardinal symptoms”.<sup>1</sup> Sputum purulence is most commonly defined as a change in sputum color from clear or white to yellow-green tinted, reflecting the increase in myeloperoxidase from neutrophils.<sup>6</sup> Not all people who have the three “cardinal symptoms” require antibiotics and biomarkers such as procalcitonin may be useful in determining who is most likely to benefit.

Comparisons of available trial data regarding the role of antibiotics are difficult as studies have evaluated different populations and employed varying inclusion and exclusion criteria, endpoints and length of follow-up. A 2012 Cochrane review found an increase in successful treatment of AECOPD in hospitalized patients who received antibiotics; however, this was not associated with improvements in length of stay or mortality for the majority of patients. The only population that showed a well-defined benefit in length of stay and mortality were critically ill patients, suggesting that they are the patients most likely to benefit from antibiotics.<sup>7</sup> In the absence of other signs of infection, patients admitted to general medical units who present with AECOPD of mild to moderate severity are not likely to benefit and should not receive antibiotics. Antibiotics are not recommended in patients who lack sputum purulence as the treatment failure rate has been reported at <10% of patients in this group.<sup>8</sup>

In patients with AECOPD who meet the criteria for antibiotic therapy, adequate coverage of common respiratory pathogens such as *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* is essential. Coverage of atypical organisms is not generally required unless specific clinical criteria suggest these pathogens are present. Patients with more advanced disease or frequent exacerbations may also need coverage of *Pseudomonas aeruginosa*. Antibiotics recommended by the GOLD guidelines include agents such as amoxicillin/clavulanate, azithromycin or doxycycline unless coverage of more resistant organisms is required based upon clinical factors (see Table 1 below). In patients with antibiotic use in the past 30 days or recurrent disease, use of an antibiotic in a different class and/or a pulmonary consultation should be considered. Recent literature supports a duration of therapy of 5 days for most patients, but longer courses (7-10 days) may be considered in severe exacerbations. Again, PCT monitoring has been shown to be a safe and effective method for deciding when to discontinue antibiotics.

In July of 2016, the FDA released a safety announcement for the fluoroquinolone class. This class of drugs now has a black box warning for serious side effects such as CNS effects, peripheral neuropathy and tendonitis or tendon rupture that may not be reversible.<sup>9</sup> The FDA also recommends against the use of fluoroquinolones for less severe infections, including acute bacterial exacerbations of chronic bronchitis. Therefore, fluoroquinolones are not recommended for AECOPD unless the patient has a severe beta-lactam allergy and no other treatment options are available.

**Table 1. Risk Factors for Resistant Bacteria Based on Exacerbation Severity**

Patient Characteristics*	Respiratory Failure Signs <sup>1</sup>	Potential Resistant Pathogens Encountered <sup>10-12</sup>
<p><b>Mild</b></p> <ul style="list-style-type: none"> <li>• FEV<sub>1</sub> &gt;50% predicted</li> <li>• &lt;3 exacerbations/year</li> <li>• No AECOPD hospitalizations (past year)</li> </ul>	<ul style="list-style-type: none"> <li>• None</li> </ul>	<ul style="list-style-type: none"> <li>• None significant</li> </ul>
<p><b>Moderate</b></p> <ul style="list-style-type: none"> <li>• FEV<sub>1</sub> 36-50% predicted</li> <li>• ≥ 3 exacerbations/year</li> <li>• 1 AECOPD hospitalization/year</li> <li>• ≥65 years of age</li> </ul>	<p><b>Non-life-threatening:</b></p> <ul style="list-style-type: none"> <li>• Accessory muscle use</li> <li>• RR &gt;30 breaths/minute</li> <li>• Hypoxemia improved with nasal cannula or Venturi mask ≤35%</li> <li>• Hypercarbia with PaCO<sub>2</sub>&lt;60 mmHg</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Haemophilus influenzae</i>, <i>Moraxella catarrhalis</i> (beta-lactamases)</li> <li>• Resistant pneumococci</li> </ul>
<p><b>Severe</b></p> <ul style="list-style-type: none"> <li>• FEV<sub>1</sub> ≤35% predicted</li> <li>• ≥ 3 exacerbations/year</li> <li>• ≥ 2 AECOPD hospitalizations/year</li> <li>• ≥ 65 years of age</li> </ul>	<p><b>Life threatening (above signs + any of the following):</b></p> <ul style="list-style-type: none"> <li>• Altered mental status</li> <li>• Acute hypercapnia (pH ≤7.25 or PaCO<sub>2</sub> &gt;60mmHg)</li> <li>• Hypoxemia not improved with nasal cannula or requiring &gt;40% Venturi mask</li> <li>• Mechanical ventilation (including non-invasive)</li> </ul>	<p>As above + evaluate risk factors for <i>Pseudomonas aeruginosa</i>:</p> <ul style="list-style-type: none"> <li>• Presence of bronchiectasis</li> <li>• Antibiotics in past 90 days</li> <li>• Prior <i>Pseudomonas</i> respiratory culture</li> <li>• History of intubation</li> <li>• Chronic steroids</li> <li>• Frequent exacerbations</li> <li>• Residence in a skilled nursing or long-term care facility</li> </ul>

\* FEV<sub>1</sub> = Forced expiratory volume 1 second; utilize previously documented FEV<sub>1</sub> (spirometry not recommended during AECOPD)

## PREVENTION OF AECOPD:

### Immunizations

Current guidelines recommend that patients with COPD receive an annual influenza vaccine and appropriate pneumococcal vaccines (PCV13 and PPSV23) as vaccination may help to reduce exacerbations and/or the risk of

hospitalization due to AECOPD.<sup>1,5</sup> It is recommended that immunization status in patients with COPD be reviewed during admission to the hospital. Vaccines may be administered in appropriate patients or recommendations should be provided to the patient's primary care provider at discharge. For further information on pneumococcal vaccine recommendations, please refer to the guidance document "Adult Pneumococcal Vaccine Recommendations" on the clinical pathways section of the ASP website or the current Centers for Disease Control and Prevention Advisory Committee on Immunization Practice guidelines.

### **Antibiotics**

Prevention of AECOPD is an important part of the management of COPD. As bacteria are known to cause exacerbations, there have been several trials conducted to determine if preventative antibiotics could decrease the exacerbation frequency and define the population that might derive greatest benefit from such therapy. Azithromycin has been studied as it has shown benefit in other pulmonary conditions.

Azithromycin is a macrolide antibiotic that binds to the 50S ribosomal subunit. The medication has bacteriostatic activity at standard dosing, although it can exhibit bactericidal activity for some infections at higher doses. Additional benefits of macrolides such as azithromycin include inhibition of several pro-inflammatory interleukins and biofilm formation in patients with *Pseudomonas aeruginosa*.<sup>13</sup>

Two randomized trials have been published regarding azithromycin for prevention of AECOPD. Comparison of data from these studies is difficult as they employed different dosing strategies, follow-up times, endpoints and populations. The first study was published by Albert et al. and was a multicenter study of patients with COPD who had required steroids and/or oxygen and admission to the emergency room or hospital within the previous year.<sup>14</sup> Patients in the intervention group received azithromycin 250 mg po daily for 1 year. Later, the COLUMBUS study was conducted at a single center in patients with  $\geq 3$  exacerbations of COPD per year.<sup>15</sup> Patients with evidence of concomitant pulmonary disease or bronchiectasis were excluded. Patients in the intervention group received azithromycin 500 mg po three times weekly for 1 year. Both studies showed a significant increase in the time to first exacerbation (266 vs 174 days,  $p < 0.001$ <sup>14</sup> and 130 vs 59 days,  $p = 0.001$ <sup>15</sup>) and rate of acute exacerbation ( $p < 0.001$  and  $p = 0.001$ , respectively). The COLUMBUS study assessed other clinical outcomes and found no significant difference in mean time-to-first admission, rate of hospital admission, or treatment of severe exacerbations with antibiotics. Neither study showed a significant difference in quality of life scores (collected using the St. George's Respiratory Questionnaire). Macrolide resistance was monitored in both studies; however, only the study by Albert et al. found a significant increase in the incidence of macrolide-resistant colonization in the intervention group (81% vs 41%,  $p < 0.001$ ).<sup>14</sup> The COLUMBUS study likely did not have had an adequate number of sputum samples to evaluate resistance and actually reported a higher percentage of resistance in the placebo group (6% vs 24%,  $p = 0.036$ ).<sup>15</sup>

There have also been some safety concerns with prolonged use of azithromycin. In the study by Albert et al., patients in the azithromycin group were more likely to experience a decrease in hearing (25% of patients,  $p = 0.04$ ).<sup>14</sup> Of the eighty patients with hearing changes who had follow-up, twenty-seven patients did recover from these hearing changes, including six patients who continued on azithromycin. The clinical significance of this finding is unclear and requires further study. While these two studies did not assess the risk of cardiac adverse effects, the risk of QTc prolongation with azithromycin has been described in the literature<sup>13</sup> and seems to be highest with patients who have other QTc-prolonging therapies or risk factors for cardiac events.

Based on the available literature, azithromycin prophylaxis cannot be routinely recommended. There is some evidence that patients with advanced age, mild disease and/or non-smoking status<sup>13</sup> may confer more benefit from such therapy; however, most of this data comes from a subgroup analysis and is insufficient to routinely warrant use. Until more information regarding the duration of prophylaxis, optimal dosing regimen and ideal

patient population is available, the risks of azithromycin prophylaxis, including cardiac effects (cardiovascular death or QTc prolongation), hearing changes and macrolide resistance likely outweigh the benefit for the majority of COPD patients. In patients who present with multiple exacerbations, consultation with a pulmonary specialist is recommended to determine the best course of therapy.

## References

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