Differential Diagnosis of Suspected Chronic Obstructive Pulmonary Disease Exacerbations in the Acute Care Setting
Best Practice

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Abstract

Patients with chronic obstructive pulmonary disease (COPD) may suffer from acute episodes of worsening dyspnea, often associated with increased cough, sputum, and/or sputum purulence. These exacerbations of COPD (ECOPDs) impact health status, accelerate lung function decline, and increase the risk of hospitalization. Importantly, close to 20% of patients are readmitted within 30 days after hospital discharge, with great cost to the person and society. Approximately 25% and 65% of patients hospitalized for an ECOPD die within 1 and 5 years, respectively. Patients with COPD are usually older and frequently have concomitant chronic diseases, including heart failure, coronary artery disease, arrhythmias, interstitial lung diseases, bronchiectasis, asthma, anxiety, and depression, and are also at increased risk of developing pneumonia, pulmonary embolism, and pneumothorax. All of these morbidities not only increase the risk of subsequent ECOPDs but can also mimic or aggravate them. Importantly, close to 70% of readmissions after an ECOPD hospitalization result from decompensation of other morbidities. These observations suggest that in patients with COPD with worsening dyspnea but without the other classic characteristics of ECOPD, a careful search for these morbidities can help detect them and allow appropriate treatment. For most morbidities, a thorough clinical evaluation supplemented by appropriate clinical investigations can guide the healthcare provider to make a precise diagnosis. This perspective integrates the currently dispersed information available and provides a practical approach to patients with COPD complaining of worsening respiratory symptoms, particularly dyspnea. A systematic approach should help improve outcomes and the personal and societal cost of ECOPDs.

Keywords: COPD; differential diagnosis; symptom flare-up; algorithms

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CONCISE CLINICAL REVIEW

At a Glance Commentary

Scientific Knowledge on the Subject: Patients with chronic obstructive pulmonary disease (COPD) frequently have concomitant morbidities that not only increase the risk of subsequent exacerbations of COPD (ECOPDs) but can also mimic or aggravate ECOPDs. A careful search can help detect these and allow for appropriate treatment.

What This Study Adds to the Field: For most morbidities that can mimic or aggravate ECOPDs, recent advances on the basis of a thorough clinical evaluation supplemented by clinical investigations can help the clinician to make precise diagnoses. This perspective integrates the currently dispersed information available and provides clinicians with a practical approach to patients with COPD complaining of worsening respiratory symptoms, particularly dyspnea. A systematic approach should help improve outcomes and the personal and societal cost of ECOPDs.

The course of chronic obstructive pulmonary disease (COPD) is punctuated by acute worsening of dyspnea, often associated with increased cough, sputum volume, and/or purulence (1, 2). These exacerbations of COPD (ECOPDs) worsen health status, accelerate lung function decline, and increase the risk of subsequent ECOPDs, hospitalization, and death (1).

Patients with COPD are usually older (3) and have multiple morbidities, including heart failure (HF), ischemic heart disease (IHD), arrhythmias, interstitial lung diseases (ILDs), bronchiectasis, anxiety, and depression, all of which increase the risk of ECOPDs and death (4). Furthermore, the incidence of pneumonia, pneumothorax, and pulmonary embolism (PE), which can mimic and/or worsen an ECOPD, are frequent in these patients (1, 3–5).

Approximately 25% and 65% of patients hospitalized for an ECOPD die within 1 and 5 years, respectively, mainly because of respiratory and cardiovascular complications, with close to 20% readmitted within 30 days after discharge (1, 5, 6). Importantly, close to 70% of these readmissions are because of decomposition of other morbidities (3, 7).

We previously proposed an updated definition of ECOPDs that, in addition to symptom worsening, incorporates the measurement of six objective variables (respiratory and cardiac rate, oxygen saturation, dyspnea, C-reactive protein [CRP], and, when available, arterial blood gases) to determine ECOPD severity (8). In most patients, especially in the milder cases seen in primary care, a classic presentation may be confidently diagnosed as an ECOPD. However, in some, particularly the more severe cases seen in the acute care setting, decomposition of coexisting morbidities (particularly HF) or development of new morbidities (e.g., PE or pneumonia) can be confused with, or contribute to, ECOPDs.

Studies have shown that directed clinical evaluation (pretest probability) complemented with clinical investigations can help precise diagnoses. This review integrates the dispersed information from those studies to provide clinicians with a practical approach to patients with COPD who have worsening respiratory symptoms, particularly dyspnea, not explained by an ECOPD who are seen primarily in the acute care setting. Despite the concerns of potential adverse drug effects, a diagnosis of ECOPD should not alter the treatment of any associated morbidity, which should adhere to the general concept of guideline-directed medical treatment (9).

Methods

This is an expert consensus by the same group that proposed the Rome definition and severity classification of ECOPD (8), expanded to include additional experts from Europe (D.S.) and South America (M.M.d.O.). These 18 experts, representing 10 countries and three continents, were divided into four groups to perform literature reviews, with particular emphasis on guidelines and expert consensus documents. Of the many morbidities that may present with respiratory symptoms resembling ECOPDs, a five-round Delphi process resulted in agreement on 12 (8). These were selected to be included in this practice guide, the contents of which were developed on the basis of the literature review per group. The groups developed an overarching algorithm and a series of detailed algorithms for the most important of these, intended to be of practical use for healthcare providers. This material was combined by the coordinators (B.R.C. and L.M.F.) and was discussed and agreed on by all members of the project. In this document, patients are defined as confirmed COPD when there is spirometric support (1) and suspected COPD if there is no spirometric confirmation but a history of exposure to tobacco smoke and/or environmental pollutants, chronic respiratory symptoms, and/or patients are receiving pharmacological treatment for COPD (10).

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Author Contributions: B.R.C. and L.M.F. developed the original concept for this work, including the organization of the methodology on which the content is based. All authors contributed to the literature searches and the virtual discussions. The first draft of the manuscript was written by B.R.C., with all authors then providing intellectual input. All authors approved the final version.

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This article has an online supplement, which is accessible from this issue’s table of contents at www.atsjournals.org.
Table 1. The CASE (Complete, Assess, Severity, Establish) Approach to a Patient with Confirmed or Suspected Chronic Obstructive Pulmonary Disease Who Presents with Worsening Respiratory Symptoms

<table>
<thead>
<tr>
<th>Complete</th>
<th>A thorough clinical assessment for evidence of underlying COPD and potential respiratory and nonrespiratory concomitant diseases, including consideration of alternative causes for the patient’s symptoms and signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess</td>
<td>Symptoms: Severity of dyspnea using a tool such as the dyspnea visual analog scale; documentation of the presence and characteristics of cough and sputum. Presence of pain and its characteristics.</td>
</tr>
<tr>
<td></td>
<td>Signs: Tachypnea, tachycardia, arrhythmia, fever, sputum volume and color, respiratory distress (accessory muscle usage), abnormalities on thoracic examination, and thorough physical examination.</td>
</tr>
<tr>
<td>Severity</td>
<td>Evaluate by combining symptoms and signs and appropriate additional investigations such as pulse oximetry. If available, obtain laboratory assessments (e.g., CRP), chest X-ray, electrocardiograph, and/or arterial blood gases.</td>
</tr>
<tr>
<td>Establish</td>
<td>Cause of the event (viral, bacterial, environmental, poor treatment adherence, alternative diagnosis, or other).</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein.

**Initial Evaluation**

A careful medical history and physical examination complemented by the rational measurement of objective variables can help establish, with a degree of certainty, that an ECOPD is the most likely diagnosis (Table 1), particularly in patients with mild events seen in the outpatient setting. However, in many patients, the signs and symptoms of an ECOPD (especially if more severe) are not specific, and other diseases may mimic an ECOPD and/or aggravate its clinical presentation (Figure 1). Most of these patients are seen in an acute care setting, and we developed an initial practical algorithm to help reach a more precise diagnosis (Figure 2).

**Cardiovascular Morbidities**

Cardiovascular morbidities are frequently present in patients experiencing ECOPDs, and thus a patient history is important to assess their presence or impact (11, 12). Chest pain/discomfort, fluid retention, or irregular pulse suggest a cardiovascular cause as an alternative or contributing diagnosis to an ECOPD.

**Acute HF**

Acute HF is defined by worsening of dyspnea at rest (particularly while supine) or during exertion and/or fatigue, together with signs of fluid retention such as pulmonary congestion, increased jugular vein distension, or ankle swelling, with objective evidence of an abnormality of the structure or function of the heart (13). Some of these clinical findings can make distinguishing ECOPD from acute HF difficult (14). In addition, COPD is present in up to 50% of patients with HF, and HF occurs in roughly 20% of individuals with COPD because of overlapping risk factors (aging and smoking) and underlying mechanisms (systemic inflammation, endothelial dysfunction, and muscular atrophy). Furthermore, an HF diagnosis is often difficult to confirm in patients with preserved ejection fraction, which is common in patients with COPD (12, 14). Hypoxemia and tachycardia in ECOPD can promote decompensation in HF, whereas pulmonary fluid retention in HF can worsen airway obstruction (12). In addition, wheezing is common in acute HF (approximately 30%) (15), whereas COPD can mask the presence of basilar crackles. However, their presence, coupled with evidence of leg edema, elevated jugular venous pressure, and a third heart sound increases the likelihood of HF being the cause of, or a contributor to, the acute event (15).
A chest X-ray can help distinguish an ECOPD from acute HF, with cardiomegaly supporting structural heart damage and HF likely present if there is pulmonary edema (16). The best laboratory markers of HF are elevation of natriuretic peptides (brain natriuretic peptide and N-terminal pro-brain natriuretic peptide) (17–19), with thresholds supportive of acute HF, consistent with European Society of Cardiology Guidelines on HF, shown in Figure 3 (20). Importantly, natriuretic peptides are commonly elevated in patients with stable COPD or pneumonia and increase further in patients with ECOPD even without acute HF (17, 19, 20). As such, higher thresholds are needed to accurately diagnose concomitant acute HF and ECOPD. More informative is the presence of low peptide concentrations, which have excellent negative predictive value for acute HF, even in patients with an ECOPD (17). Patients with elevated natriuretic peptides during an ECOPD have a worse prognosis, including a risk of death (21). Finally, point-of-care ultrasonography can help differentiate ECOPD from acute HF, although more research is required to establish their impact on health outcome benefits (19, 20). A diagnostic algorithm to evaluate a patient with suspected acute HF is shown in Figure 3.

**IHD**

Underlying IHD is associated with more prolonged ECOPDs (22). Myocardial injury is common and clinically significant during ECOPDs, particularly in patients with pre-existing IHD (23), and an ECOPD significantly increases the risk of myocardial infarction and stroke, not only in the first 30 days after an ECOPD (by 4–10 times) but for up to 1 year after the event (24, 25). Moreover, one-third of patients with IHD have COPD, which is associated with more frequent emergency room visits (26), with COPD independently increasing IHD risk and heightening morbidity and mortality (12, 27).

In outpatients presenting with an ECOPD, a clinical history (established IHD), current symptoms (chest pain/discomfort and/or palpitations), and signs of systemic atherosclerosis (carotid bruit and/or reduced peripheral pulses) or those consistent with acute myocardial ischemia (diaphoresis and/or third heart sound), suggest concomitant IHD. Symptoms plus an abnormal resting electrocardiogram (ECG) support the presence of acute myocardial ischemia. Nevertheless, the diagnosis of myocardial injury or infarction, either as an independent or contributing morbidity of an ECOPD, should follow the fourth universal definition criteria (28). This requires elevation in blood troponin at admission and/or increase during follow-up, plus at least one other factor (symptoms and/or new ECG changes). COPD can be associated with chronic (usually stable) elevations in troponin concentrations, which can increase during an ECOPD. The diagnostic approach for a patient with suspected IHD is shown in Figure E1 in the online data supplement (29). No troponin thresholds are quoted because of variability across laboratories and methodology. When the clinical suspicion of IHD is high, a guideline-directed evaluation is generally warranted. Furthermore, given the high prevalence of IHD with ECOPD, evaluation for atherosclerosis and associated diseases should always be considered (29, 30).
Arrhythmias

The prevalence of cardiac arrhythmias, especially atrial fibrillation (AF), is increased in patients with COPD. Furthermore, during an ECOPD, the risk of AF and other arrhythmias doubles (12, 31), and importantly, AF during an ECOPD increases morbidity and mortality (31). AF presence can be ascertained by atypical chest discomfort, palpitations, lightheadedness, and dyspnea, as well as an irregular pulse on palpation. Unlike other morbidities, there is less diagnostic dilemma between AF and ECOPD. Standard ECG and heart monitoring can detect the presence of chronic, acute, or intermittent arrhythmias (32). The role of new-onset AF as a cause of acute dyspnea in a patient with COPD is still unknown, so the unresolved clinical question is whether AF was a pre-existing or new-onset event (1, 32). The diagnostic approach to a patient with suspected AF is shown in Figure E2.

PE

The prevalence of PE in patients with ECOPD ranges from 3.3% to 29.4% (33), being more common in patients with atypical or unexplained ECOPD and requiring specific and prompt management to improve outcomes (34). PE should be considered in patients with increased dyspnea in the context of risk factors such as a history of venous thromboembolic disease, hospitalization for HF, or malignancy (34, 35). Although patients with either PE or ECOPD characteristically complain of worsened dyspnea, those with PE commonly report pleuritic chest pain, hemoptysis, and signs of right HF and are less likely to have a cough with increased or purulent sputum.

Two studies have considered practical approaches to evaluating PE frequency in hospitalized patients with ECOPD (36, 37). The first used the revised Geneva score to assess the pretest clinical probability of PE in 740 patients, whether PE was suspected or not (36). Patients with a high clinical probability of PE (score of at least 11) proceeded to computed tomography (CT) pulmonary angiogram (CTPA) and leg ultrasound. For patients scoring under 11, D-dimer testing was performed, with PE excluded (and no subsequent testing) if the D-dimer value was less than 500 ng/ml. Of 17 patients with high pretest probability, 5 had positive CTPA. In the 442 with low pretest probability and D-dimer of at least 500 μg/L, 36 had a positive CTPA. Importantly, 3-month mortality when PE or deep-vein thrombosis (DVT) was excluded was 5.5%, compared with 27% and 20% in patients with confirmed PE or isolated DVT, respectively.

In the second study, usual care plus an active strategy for diagnosing PE was compared with usual care alone in 746 patients not suspected of having a PE by the physician in charge who were hospitalized because of an ECOPD (37), the primary outcome being a composite index of nonfatal venous thromboembolism, COPD readmission, or death within 90 days. Patients in the intervention group underwent D-dimer testing, with a negative D-dimer value (less than 500 ng/ml) used to exclude PE. A CTPA was performed only in patients with positive D-dimer value.

Figure 3. Algorithm reflecting the clinical features of a patient with chronic obstructive pulmonary disease (COPD) presenting with increased respiratory symptoms and suspected acute heart failure. Recommendations are on the basis of the most recent European and American Guidelines on heart failure (19, 20). *The thresholds for N-terminal pro-brain natriuretic peptide (NT-proBNP) and BNP are intended for the diagnosis of acute heart failure (HF) (20) and may need correction with age. Thresholds for new onset stable HF are much lower (i.e., NT-proBNP >125 pg/ml and BNP >35 pg/ml) (19) and should be used outside the context of an exacerbation of COPD. Note that the presence of COPD may raise these values. Please see text for further details. ECG = electrocardiogram; ECOPD = exacerbation of chronic obstructive pulmonary disease; GDMT = guideline-directed medical treatment; HJ reflux = hepatojugular reflux; JVD = jugular vein distention; PND = paroxysmal nocturnal dyspnea; WBC = white blood cell count.
Figure 4. Algorithm reflecting the clinical features of a patient with COPD presenting with increased respiratory symptoms and suspected pulmonary embolism (PE). Recommendations are on the basis of Konstantinides and colleagues (35) and Couturaud and colleagues (36). *PE probability assessed using Geneva or Wells scores. COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; CTPA = computed tomography pulmonary angiogram; DVT = deep-vein thrombosis; ECOPD = exacerbation of chronic obstructive pulmonary disease; GDMT = guideline-directed medical treatment; WBC = white blood cell count.

with a positive D-dimer value. The primary outcome was similar in the two groups (29.7% and 29.2% in the intervention and control groups, respectively).

These studies show that in patients hospitalized with an ECOPD, overall PE prevalence is around 4–6% (36, 37). In patients with suspected PE, the prevalence of venous thromboembolism was 11.7% and 4.3% among those in whom PE was not suspected (36). Given the high mortality with PE, evidence supports CTPA imaging in patients with a high clinical PE pretest probability (Geneva score of at least 11) and an atypical clinical presentation for ECOPD, with no need to assess D-dimer concentrations. If the pretest probability is low (Geneva score less than 11), a D-dimer less than 500 ng/ml would support ECOPD as the diagnosis and help avoid imaging testing. In addition, lower-limb compression ultrasonography (CUS) can diagnose DVT in patients with a negative CTPA (or when CTPA is contraindicated) (35). In the setting of suspected PE, CUS can be limited to a simple four-point examination (bilateral groin and popliteal fossa) (35). The probability of a positive proximal CUS in suspected PE is higher in patients with signs and symptoms related to the leg veins than in asymptomatic patients (38). The diagnostic approach for a patient with suspected PE is shown in Figure 4.

Infectious Diseases

Pneumonia

In patients with COPD, the symptoms of pneumonia and ECOPD may be similar (worsened cough, sputum production, dyspnea, and fever) (39). Physical examination may help in the differentiation, with signs of consolidation (localized crackles, crepitus, and dullness on percussion) more frequent in patients with pneumonia. However, because a diagnosis of COPD increases pneumonia risk (by 1.3- to 13.5-fold) and severity (40), pneumonia should always be considered in the differential diagnosis of patients with symptoms of ECOPD.

If the clinical assessment deems the ECOPD to be mild or moderate and there are no signs of lung consolidation, no further diagnostic testing to differentiate the two diseases is indicated. However, if the episode is severe and/or prolonged (41), and there are abnormal chest exam findings, a proper diagnosis of pneumonia should be undertaken. Mortality after hospitalized pneumonia is higher than after hospitalized ECOPD (42). Although most patients without severe ECOPD can be safely treated on the basis of chest X-ray results alone, opacities not visible on a chest X-ray may be seen with more sensitive CT scans (43, 44).

Serum biomarkers are becoming increasingly available as point-of-care tests and are readily obtainable in emergency rooms or hospitals. Higher CRP values are more likely to support a diagnosis of pneumonia, particularly of bacterial etiology, rather than ECOPD (45). The role of procalcitonin is less clear, with evidence suggesting that in patients with a low pretest probability for pneumonia, a low procalcitonin value supports a nonbacterial etiology for the process (46, 47). Other potentially useful biomarkers include IL-6, white blood cell count, and platelets, although no cut-off values have yet been validated (48).

In a patient with an ECOPD, respiratory syncytial virus, severe acute respiratory
 syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]), or influenza as the causing agent should be considered, on the basis of the prevalence of these viruses in the community and the season, as specific treatments are available and patients with COPD are good candidates for these interventions (49). Sputum purulence is a clinical biomarker that supports bacterial infection and predicts the benefit of treatment with antibiotics (50). In patients with severe ECOPD or pneumonia, sputum gram staining and cultures and molecular point-of-care testing (51) can help guide antibiotic therapy, as difficult-to-treat bacterial pathogens can often be present in these patients. The presence of pneumonia should also prompt urine tests for pneumococcal and Legionella antigens. The diagnostic approach for a patient with suspected pneumonia is shown in Figure 5.

**Bronchiectasis**
Bronchiectasis prevalence in patients with COPD varies from 8% to 69%, being higher in those with more severe airflow obstruction (52). Patients with overlapping COPD and bronchiectasis have more exacerbations and symptoms, a higher risk of pneumonia, and increased mortality than patients with either diagnosis. This increased exacerbation risk may be because of more frequent isolation of pathogenic bacteria, including *Pseudomonas aeruginosa* (53).

The diagnosis of COPD is primarily physiological, whereas that of bronchiectasis is radiological. However, patients with severe and/or extensive bronchiectasis can have poorly-reversible airflow obstruction, meeting spirometric criteria for COPD. Diagnostic criteria for COPD/bronchiectasis overlap include appropriate ROSE (radiology, airflow obstruction, symptoms, and exposure) (54). In these patients, it is impossible to differentiate exacerbation of the bronchiectasis from ECOPD. Bronchiectasis guidelines recommend searching for an alternative treatable underlying cause (such as antibody deficiency) (55), and it is logical to use CT scans to exclude bronchiectasis in patients with frequent ECOPDs (1).

**Inflammatory Morbidities**

**Asthma Exacerbation**
The prevalence of comorbid bronchial asthma in patients with COPD ranges from 3.8% to 38.8% depending on the definitions used (56), with a family history of asthma, younger age, and the presence of atopy or childhood asthma suggesting comorbid asthma in a patient with COPD. Patients with both diseases are more symptomatic, have poorer lung function, and are at increased risk of exacerbation and hospitalization compared with patients with either disease (56, 57).

No publication has addressed whether exacerbations in patients with comorbid COPD and asthma are different from exacerbations of asthma or ECOPD, and guidelines define asthma exacerbations and ECOPDs similarly (1, 57). The most frequent cause of both ECOPDs and asthma exacerbations are viral infections and/or pollutants, and although sputum/purulence, one of the typical features of ECOPD, could help distinguish the two events, sputum/purulence has also been reported in asthma exacerbations. Thus, the management of concomitant COPD and asthma is similar to that of asthma (1, 57).
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ILDs
ILDs occur in approximately 8% of individuals with tobacco smoke exposure (58). Despite marked differences in static respiratory mechanics between ILDs and COPD, patients with both diseases characteristically describe dyspnea and dry cough as their major symptoms, with dyspnea likely because of an uncoupling between the effort needed to breathe and the effective expired volume of inspired air (59). As in COPD, the natural course of ILDs (especially idiopathic pulmonary fibrosis [IPF]) is punctuated by exacerbations, usually severe, which are associated with clinical deterioration, although IPF exacerbations have a worse prognosis than ECOPDs (60).

Some patients may present with combined pulmonary fibrosis and emphysema (61). When these patients experience an exacerbation, it may be difficult to differentiate an ECOPD from an IPF exacerbation (62). The evidence of new widespread alveolar abnormalities (ground-glass) in imaging studies in a patient with symptoms consistent with ECOPD supports an important role of an ILD exacerbation in the patient’s event (60).

Miscellaneous Morbidities

Anxiety and Depression
In patients with ECOPD, the prevalence of depression and anxiety ranges between 9% and 58%, depending on the assessment method (63). Furthermore, patients with COPD who have depression and/or anxiety are at increased risk of ECOPD and hospitalizations compared with nondepressed individuals (64). In addition, nearly 10% of current and former smokers have concomitant anxiety and depression, which independently predict the risk of exacerbations (65). This vicious cycle worsens with every exacerbation, as each episode leads to symptom worsening, aggravates muscle weakness, and decreases functional capacity (limiting activity), consequently worsening anxiety and depression (63, 64, 66).

The causal role of anxiety/depression in ECOPDs has not been systematically studied. Panic attacks and anxiety may cause tachypnea that, in COPD, may result in hyperinflation and culminate in acute hypercapnic respiratory failure (67). Furthermore, hypercapnia triggers panic attacks because of the activation of specific brainstem reflexes (68), causing hyperventilation, hyperinflation, and aggravating panic symptoms (67). In patients with COPD who have a panic attack, the lack of increase in cough and sputum in the absence of either an inflammatory burst or another explanatory morbidity for dyspnea and tachypnea can help establish a diagnosis.

Pneumothorax
Pneumothorax is a potentially life-threatening event that occurs in some patients with COPD, resembles an ECOPD, and requires prompt recognition. Subpleural blebs and bullae are frequent in older males with more severe emphysema and cigarette or marijuana smoke exposure (69, 70). In patients with COPD who present with pneumothorax, dyspnea is associated with chest pain, often accompanied by hypoxemia, and occasionally, acute respiratory failure (71). A pneumothorax diagnosis is usually confirmed by chest X-ray, being careful to avoid misinterpretation with bullae. Lung ultrasound may also be diagnostic and more readily available in the ICU or emergency room settings (72).

Pleural Effusion
Large pleural effusions may contribute to worsening dyspnea in patients with COPD (73), as they alter lung and chest wall elastic equilibrium, creating a restrictive ventilatory defect. If the effusion is large and associated with elevated natriuretic peptides, the causes are more likely cardiovascular in origin, particularly acute HF (74), whereas if it is associated with high CRP concentrations, it likely reflects a parapneumonic effusion or empyema because of underlying infection (71, 74) and occasionally lung cancer (71). Chest X-rays, ultrasound imaging, and chest CT are all useful in determining the presence, size, and complexity of pleural effusion in a patient with ECOPD (71, 75).

Anemia
Hemoglobin assessment is important in patients with COPD. Polycythemia can indicate untreated hypoxemia, whereas anemia, a frequent concomitant morbidity in stable COPD with a prevalence of 5–30% (76), may contribute to breathlessness. Patients with anemia tend to be older, with worse airflow limitation and a higher burden of cardiac and metabolic comorbidities than nonanemic patients (76). There is an association between anemia and elevated CRP concentration, a cytokine often augmented during an ECOPD (77). Although there does not appear to be a relationship between the presence of anemia and ECOPD incidence, it seems logical that coexistent anemia may worsen the dyspnea that is characteristic of such episodes and so impact ECOPD severity. Patients with comorbid COPD and anemia tend to have longer hospital stays and are at increased risk of death, perhaps through association with comorbidities (77).

Conclusions
Combining a thorough clinical history and examination with currently available clinical biomarkers, most patients with COPD who have a classic presentation may be diagnosed with reasonable confidence as having an ECOPD. However, in other patients, acute decompensations of coexisting morbidities or the development of acute events such as acute HF, pneumonia, or PE can contribute to or cause those events. Thus, all patients with COPD who have worsening respiratory symptoms, particularly dyspnea with more severe emphysema and cigarette or marijuana smoke exposure (69, 70), are at increased risk of death, perhaps through association with comorbidities (77).
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