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WHAT IS A COPD EXACERBATION? CURRENT DEFINITIONS, PITFALLS, CHALLENGES AND OPPORTUNITIES FOR IMPROVEMENT

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a chronic illness that may be periodically punctuated by exacerbations, characterized by acute worsening of dyspnea, and/or cough and sputum production, and/or increased sputum purulence. COPD exacerbations are common and carry with them important clinical and economic consequences including lost work productivity, increased utilization of health care resources, temporary or permanent reductions in lung function and exercise capacity, hospitalization, and sometimes death. Over the past two decades, clinicians and researchers have broadened their goals of treatment of COPD to extend beyond improving lung function and symptoms and have also begun to address the importance of prevention and reduction of exacerbations. However, despite the best efforts of clinicians and guideline committees, current definitions of exacerbations of COPD are imperfect and fraught with problems. The cardinal symptoms of an exacerbation of COPD are nonspecific and can result from acute cardio-respiratory illnesses other than COPD. A proposed definition, which may be more specific than current definitions, suggests that COPD exacerbation be defined as an acute or sub-acute worsening of dyspnoea (≥5 using a 0–10 scale) sometimes but not necessarily accompanied by increased cough and/or sputum volume or sputum purulence. Necessary laboratory criteria for an exacerbation include: oxygen desaturation ≤4% below that of stable state, elevated circulating blood neutrophils or eosinophils (≥9000 neutrophils per mm^3 or ≥ 2% blood eosinophils), and elevated CRP (≥3 mg/L), without evidence of pneumonia or pulmonary edema on the chest radiograph, and negative laboratory tests supportive of other etiologies. Herein, we will discuss the current state of the art with respect to how we define COPD exacerbations, associated pitfalls and challenges, and opportunities for improvement.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a chronic illness that may be periodically punctuated by acute worsening of symptoms characterized clinically by greater dyspnea, cough and sputum production, and increased sputum purulence. These acute worsening of symptoms have been termed acute exacerbations of COPD (AECOPD). COPD exacerbations are common and carry with them important clinical and economic consequences including lost work productivity, acute declines in quality of life, temporary or permanent reductions in lung function and exercise capacity, hospitalization, and sometimes death (1-7). Prospective studies have shown that the most important risk factor for future exacerbations is a patient history of prior exacerbations (8). Other risk factors for exacerbations include low baseline lung function, increased symptom burden, radiographic evidence of emphysema, and a history of chronic bronchitis (8-10).

Over the past two decades clinicians and researchers have broadened their goals of chronic COPD treatment to extend beyond improving lung function and symptoms and have also begun to address the importance of maintenance treatment of stable COPD to prevent or decrease the incidence of exacerbations. Many randomized clinical trials of chronic COPD therapies now use AECOPD event rates as their primary study outcome to judge efficacy of chronic COPD therapies (11, 12). Given the emerging clinical, economic and research importance of AECOPD, it is critical that exacerbations be rigorously defined and that exacerbation events can be easily ascertained and quantified both in clinical practice and in research studies.

It is important that we gain a better understanding of what an exacerbation is, so that we may improve upon the current accepted definitions and gain clarity on these common and sometimes life-threatening events. The objective of this narrative review will be to discuss the current state of the art with respect to how we define COPD exacerbations, associated pitfalls and challenges, and opportunities for improvement. Relevant articles for this review were retrieved from the Medline and PubMed databases using the following search terms: 'COPD exacerbation', 'exacerbations of COPD', and 'COPD exacerbation definition'. Abstracts were assessed for potential relevance to the topic and applicable articles were included in this review.

CURRENT DEFINITION

Exacerbations can be defined using symptom-based or event-based definitions, or a combination of both. Symptom-based definitions rely on patient-reporting of worsening respiratory symptoms either to a

health-care practitioner or within a symptom diary.   Typical symptoms of AECOPD would include worsening dyspnea, cough, increased sputum volume or increased sputum purulence. In contrast event-based definitions capture patients whose condition has changed enough to require a change in treatment.

The first definition of COPD exacerbation dates to the 1980's and was a symptom-based definition focused exclusively on three cardinal symptoms, namely the "increase or onset of shortness of breath, sputum production and/or sputum purulence" (13). Later an event-driven definition was introduced, and exacerbations were defined as a worsening of COPD symptoms requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids, and other bronchodilator therapy" (14). A subsequent definition proposed by a consensus conference in 2000 defined an exacerbation as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and necessitates a change in regular medication, in a patient with underlying COPD" (15). The 2018 GOLD definition of AECOPD uses an event-based definition. In the 2018 GOLD document an exacerbation of COPD is defined as "an acute worsening of respiratory symptoms that results in additional therapy". Exacerbations are classified as: 1) mild if they are treated with short-acting bronchodilators only; 2) moderate if they are treated with short-acting bronchodilators plus antibiotics and/or oral corticosteroids; or 3) severe if the patient visits the emergency room or requires hospitalization because of an exacerbation (16).

The 2018 GOLD definition integrates the concept of clinical worsening of an acute event with a change in the regular treatment for COPD. The definition includes a compromise between symptom- and event-driven approaches adopted by earlier definitions. It provides a grading system from mild to severe based on management and therapy.   Although not stated within the definition, a vague description of symptoms ('an acute worsening of respiratory symptoms') should prompt consideration of a differential diagnosis for acute events that can mimic an acute COPD exacerbation. These events may be pulmonary (eg. pneumonia, pulmonary thromboembolism, etc) or non-pulmonary in nature, (eg. congestive heart failure, acute coronary syndromes, or anemia) (17).

Advantages and disadvantages to symptom-based definitions of AECOPD:

An obvious advantage of using a symptom-based definition is that symptoms are important and are the primary concern of the patient. Therefore, defining an exacerbation based on symptoms has clinical relevance to patients and to caregivers. A further advantage is that validated tools to capture symptom-based

AECOPD's exist and include patient diary cards (18) and the validated Exacerbation of Chronic Pulmonary Disease Tool (EXACT) (19).

The disadvantages include the subjective nature of symptom-based definitions. In some cases, it is difficult for the patient and the clinician to decide if a patient's symptoms are 'increased' more than usual (19). In addition, numerous studies have shown that symptom-based AECOPDs often go unreported, leading to an under-estimation of patient exacerbation rates (20, 21). Finally, paper-based diary cards and home-based symptom assessment tools are plagued by poor adherence and recall biases related to delays in entering symptoms (diary hoarding), thus leading to retrospective record entry and reduced data accuracy (22). Use of electronic diaries, rather than paper-based methods, may allow for daily prompting of patients and may help to alleviate delays in data entry (22).

Studies of the EXACT tool confirmed that the EXACT reliably assesses symptom severity and that EXACT scores are significantly elevated at exacerbation compared to baseline, stable state values (19, 23) . Independent studies have also confirmed that EXACT scores increase at COPD exacerbation, the magnitude of which reflects the severity of the event in terms of treatment, systemic inflammation, airflow limitation and symptom recovery time (24). However, studies comparing the EXACT tool to daily patient diary cards and physician assessment have shown marked disparity in exacerbations assessments. Over a two-year period, only 28% of daily diary card exacerbations were picked up by the EXACT questionnaire, indicating poor reliability between standard tools being used to pick up symptom-based exacerbations (24).

Advantages and disadvantages to event-based definitions of AECOPD:

Event-based definitions circumvent the problems associated with identifying a group of symptoms by simply capturing patients whose condition has changed enough to require a change in treatment or hospitalization. Advantages include that event-based definitions capture exacerbations that are more clinically important compared to pure symptom-based definitions. These exacerbations are also associated with direct healthcare costs in the form of additional medications and physician visits or hospitalizations, and therefore these exacerbations are useful for economic analyses (25). Disadvantages include that event-based definitions can be confounded by patient socio-economic status, geography, and access to healthcare resources. By definition, to achieve an event a patient has to make contact with a healthcare professional and the healthcare

professional has to decide the patient warrants treatment. Those with limited access to healthcare resources, whether because of geographic isolation, immobility, or poverty, will necessarily experience fewer events (26).

Studies that have assessed the incidence of symptom-based AECOPDs compared to event-based AECOPDs in the same patients followed over time suggest that observed exacerbation rates are much higher if symptom-based definitions are used. The Investigating New Standards for Prophylaxis in Reducing Exacerbations (INSPIRE Study) compared the incidence of AECOPD using both symptom-based definitions as well as a treatment-based definition and found that the incidence rate was 3 AECOPDs/patient-year if a symptom-based definition was used and 1.5 AECOPD's/patient-year if an event-based definition was used, suggesting that 50% of symptom-defined COPD exacerbations are not treated by physicians (27).

PITFALLS AND CHALLENGES

Despite the best efforts of clinicians and guideline committees, current definitions of exacerbations of COPD are imperfect and fraught with problems. The cardinal symptoms of an exacerbation of COPD are nonspecific and can represent many disorders, including but not limited to pneumonia, congestive heart failure, acute coronary syndrome, and pulmonary embolism (17) (Table 2). Bacterial or viral infection may precede exacerbations, but in a significant proportion the inciting factor is unclear (28, 29). Additionally, exacerbations may not necessarily be limited to COPD; recent literature suggests that those at risk for COPD (i.e. those with a significant smoking history) but without airflow obstruction may suffer from a similar number of exacerbation-like events compared to those with airflow obstruction (30-33). Moreover, many exacerbations are not reported to physicians, making the true prevalence uncertain (1, 34).

The foundation of the definition of an exacerbation is the patient's perception of an increase in symptoms. Increased dyspnea has been shown in several studies to be a risk factor for exacerbations and mortality, alone and as part of a multidimensional index (35-37). However, it is possible that the perception of respiratory symptoms varies among individuals. A recent study found that those who experienced frequent exacerbations had heightened dyspnea perception during CO_2 rebreathing compared to those with infrequent exacerbations (38). How this relates to the development of exacerbations remains uncertain, and it may lead to more questions than answers. For instance, it is unclear if airway inflammation is greater in those patients with heightened dyspnea perception and if this may explain the link between dyspnea perception and elevated risk of exacerbation (29, 39).

The necessity of determining the etiology of an exacerbation remains controversial. It has been estimated that viral and bacterial infection are responsible for the majority of COPD exacerbations (Table 2). Although viral infection can be detected using rapid polymerase chain reaction-based tests (40), revealing a viral etiology may not result in a change in management outside of the identification of influenza. Additionally, the detection of bacteria in a patient with a COPD exacerbation does not necessarily distinguish a colonizing organism from a pathogen, nor does it distinguish lower respiratory tract infection from exacerbation. As such, it is not recommended by current guidelines to obtain sputum cultures as they are not always feasible or reliable, particularly in the outpatient setting (16). Moreover there are conflicting data whether antibiotics are useful in exacerbations even in the presence of sputum purulence (41-43). Newer technologies such as the electronic nose may help distinguish COPD exacerbations with concurrent infection from those without infection (44). Tools such as these are greatly needed to help guide the use of antibiotics during exacerbations.

Phenotyping of exacerbations remains imperfect; our current classification scheme does not adequately capture the diversity or complexity. It is partially addressed by the division into mild, moderate, and severe categories, which conventionally are described as requiring increased short-acting bronchodilator use, treatment with antibiotics and/or steroids, or an emergency room visit or hospitalization, respectively. The GOLD committee also recommended that severe exacerbations be subclassified into no respiratory failure, acute respiratory failure – non-life-threatening, and acute respiratory failure – life-threatening (16). However, questions regarding this classification scheme remain. For example, how do we characterize mild exacerbations, which only require an increased use of bronchodilators? Are they truly exacerbations or do they represent a slightly exaggerated increase in day to day symptom variability? What is responsible for these minor increases in symptoms? How do we categorize exacerbations that require treatment with antibiotics alone? Could these exacerbations be lower respiratory tract infections and not necessarily exacerbations of underlying COPD? Finally, none of these descriptors of COPD exacerbations specify an underlying pathophysiology.

One of the rate-limiting steps in diagnosing an exacerbation is ensuring that a physician is made aware of them. Unfortunately, many exacerbations are not reported. In one study of 128 COPD patients followed for 6 years, 1099 exacerbations identified by daily symptom diaries were recorded, however 441

(40.2%) of these diary card exacerbations were not reported to a physician (45). Another study of 61 patients found similar results (1).

Additionally, recall of exacerbations is poor. In the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS), 68 subjects with and without COPD had medical questionnaires taken at baseline and then again 6 weeks later to determine whether they had experienced AECOPDs in the previous year. There was a disparity in patient responses at baseline and 6 weeks later in 20 of 68 subjects (29%). Six patients reported more exacerbations experienced within the previous year at 6 weeks compared with at baseline, and 14 reported fewer exacerbations (46). This suggests that our definition is not specific enough for patients to identify exacerbations, and/or that patient recall of exacerbation events is faulty.

Several studies of the "frequent exacerbator" phenotype have been published recently. Although the frequent exacerbator may be responsible for a significant proportion of healthcare utilization in COPD, the true prevalence of this phenotype is not clear. In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, a history of previous exacerbations was the greatest risk factor for future exacerbations (8). However, of those with 2 or more exacerbations in the year prior to enrollment, only 58% of them had frequent exacerbations in year 1, and only 60% of those with frequent exacerbations in year 1 had frequent exacerbations in year 2. Therefore, 40-42% of the subjects had fewer than the anticipated number of exacerbations in the year following. A secondary analysis of the ECLIPSE study determined that lower lung function was associated from a switch from an infrequent exacerbator to a frequent one, but that no parameter clearly predicted a change in exacerbation frequency category (47). In a similar observational study, among 59 subjects who had mild exacerbations during the first year, 32.2% of them experienced exacerbations in the second year (48). Similarly, among 60 patients with moderate or severe exacerbations during the first year, 40% also had the same severity of exacerbation during the second year. Thus, it seems like the phenotype of the "frequent exacerbator" can vary year to year and thus does not necessarily convey a strong positive predictive value for future events.

These findings come with caveats. The definition of the "frequent exacerbator" has varied in prior literature, making it difficult to accurately summarize the data. Some studies have used a threshold of ≥3 exacerbations per year (1, 49, 50), whereas others have used a threshold as low as ≥1.5 per year (2). Additionally, recent literature has revealed that this phenotype is not quite as common as once believed. In

the SPIROMICS cohort, only 82 of 1105 subjects (7%) had at least one exacerbation per year during three years of follow-up, and only 23 (2%) had 2 or more exacerbations per year (51).

Another topic that deserves further attention is the determination of when exacerbations begin and end. Using home diary card data, an exacerbation has been defined as the first of two or more consecutive days on which the patient records two or more new or worsening respiratory symptoms (34). Aaron and colleagues used this definition and showed that in 1115 of 1995 (56%) COPD exacerbations recorded using home diary cards the onset of exacerbation was sudden and the exacerbation threshold was crossed on the same day respiratory symptoms began (52). In contrast, 44% of exacerbations were characterized by gradual onset of symptoms. Patients who experienced sudden onset exacerbations had greater mean daily symptom scores, greater peak symptom scores and shorter median recovery times back to baseline health status (11 vs 13 days, p<0.001) (52).

The hallmark of the determination of exacerbation recovery is the return of symptoms back to baseline values. A study by Wilkinson et al. defined recovery of an exacerbation as return of respiratory symptoms to baseline levels for a period of three days (45). In this study, median time to recovery was 10.7 days. A more recent study examining the utility of the EXACT found that recovery of exacerbations was approximately 12 days (53). However, an older study by Seemungal et al. found that only 75.2% of 101 patients with moderate to severe COPD had "recovery" by 35 days as defined by their peak expiratory flow, and 7.1% of them had permanent reductions in peak expiratory flow at 91 days (34). Therefore, perhaps a newer paradigm for the determination of exacerbation recovery is needed. This lends to the possibility of newer technologies such as activity and heart rate monitors, portable continuous pulse oximeters, and telemedicine as tools to not only help identify symptoms and signs that herald an impending exacerbation but also to aid in the determination of exacerbation recovery. Thus far, current literature has focused on the use of activity monitors to detect daily physical activity in COPD but not in the detection of a new exacerbation or recovery from one. (54-56).

OPPORTUNITIES FOR IMPROVEMENT

Current definitions of exacerbations of COPD are limited by the subjective nature of symptoms used to define their occurrence, the non-specificity of symptoms for pulmonary vs cardiac origin, patient non-reporting of exacerbation events to their healthcare providers, and the variable response of clinicians to the

patient's report of symptoms. The lack of an objective biomarker that indicates the onset of the event as well as its severity and prognosis is a major problem with the current definition of exacerbation. There is a need to develop a new, easy to use, and objective definition of exacerbation that incorporates symptom change with biomarker characterization. An example would be acute coronary syndromes which are diagnosed based on a patient's history of angina-type chest pain, with specific diagnostic biomarkers including characteristic findings on ECG and changes in serum cardiac troponin being used to help confirm the diagnosis and further phenotype the syndrome (myocardial infarction vs unstable angina). If symptoms of AECOPD could be combined with a sensitive and specific biomarker for AECOPD, then diagnosis of AECOPD would become less subjective and hence more reliable.

Biomarkers for AECOPD:

Unfortunately, at present, the ideal biomarker to identify AECOPD remains elusive. Acute changes in lung function (FEV_1) or the FEV_1/FVC ratio are not sensitive, and do not correlate well with AECOPD (57, 58). Commonly measured serum biomarkers such as C reactive protein (CRP) or fibrinogen are non-specific when used independently and are elevated in many other acute or chronic inflammatory or infectious states (39, 59).

Several plasma biomarkers of airway infection and inflammation have been studied in COPD exacerbations, but none has been found to be suitable for clinical use. A recent study of 86 Spanish patients hospitalized with AECOPD used multi-level network analysis to investigate pathobiological mechanisms of exacerbations and tried to identify biomarkers that can improve the specificity of the diagnosis. The investigators found that exacerbations were characterized by a disruption of the structure of the correlation network observed during convalescence, indicating less resilience and homeokinesis during exacerbations. A trio of biomarkers characterized by dyspnoea levels $\geqslant$5 (on an analogue visual score that ranges from 0 to 10), CRP $\geqslant$3 mg·L−1 and $\geqslant$70% circulating neutrophils had a specificity of 0.96, a sensitivity of 0.90, negative predictive value of 0.88 and positive predictive value of 0.97 for the identification of AECOPD (60).

Previous studies have identified four potential phenotypes of COPD exacerbations: bacterial, viral, eosinophilic, and pauci-inflammatory (67). To date highly sensitive and specific biomarkers to accurately phenotype AECOPD have proved somewhat elusive. Biomarkers associated with bacteria-driven exacerbations have poor specificity: a sputum IL-1beta of 130 pg/ml had a sensitivity and specificity of 80% and 60%

respectively, and a serum CRP of 10 mg/L had sensitivity and specificity of only 65%. Similarly, a serum eosinophil count ≥ 2% had a sensitivity and specificity of 90% and 60% to identify eosinophilic-associated exacerbations (61). At this point, accurate phenotyping of AECOPD has not proven feasible in routine clinical practice.

Recent attention has been placed on using alternative biomarkers to phenotype acute COPD exacerbations. Procalcitonin, the prohormone of calcitonin, is released in different tissues in response to bacterial, but not viral, infections or nonspecific inflammation (62). For this reason, procalcitonin can theoretically be used as a biomarker to help differentiate between COPD exacerbations caused by bacteria and exacerbations due to other etiologies. A recent meta-analysis of 8 trials evaluating 1062 patients with AECOPD demonstrated that procalcitonin-based protocols could decrease antibiotic prescription for AECOPD (RR 0.56, 95% CI 0.43–0.73) without adversely affecting clinical outcomes such as rate of treatment failure, length of hospitalization, exacerbation recurrence rate or mortality (63). In contrast, a trial of 1656 patients who presented to the ED with a suspected lower respiratory tract infection found that the provision of procalcitonin assay results, along with instructions on their interpretation, to emergency department and hospital-based clinicians did not result in less use of antibiotics than did usual care among patients with suspected lower respiratory tract infections (64). To date, it is not known whether procalcitonin based protocols are cost effective and change clinical outcomes for COPD in routine clinical practice.

A Potential New Definition for COPD Exacerbations

Table 1 shows a proposed new definition for COPD exacerbation as well as a grading system to characterize COPD clinical states. This new definition and grading system have been adapted and refined from a 'precision medicine' proposal advanced by Agusti et al (65) and from a paper by Celli et al describing grading COPD clinical states (66). Newer evidence generated by Bafadhel et al (67) and Noell et al (60) has been incorporated into the definition. According to the new proposed definition the clinical hallmarks of COPD exacerbation are increased dyspnoea (≥5 using a 0–10 scale), sometimes but not necessarily accompanied by increased cough, sputum volume, or sputum purulence. Laboratory evidence necessary to confirm a COPD exacerbation include: oxygen desaturation≤ 4% below that of stable state, elevated CRP (≥3 mg/L), and circulating blood neutrophilia (≥ 9000 neutrophils/mm) or circulating blood eosinophilia (≥ 2% blood eosinophils). Other etiologies of respiratory decompensation should be ruled out by obtaining a chest radiograph which excludes pneumonia, congestive heart failure, or pleural effusion/pneumothorax. When the

same exacerbation syndrome is accompanied by hypercapnia and acute respiratory acidosis, the syndrome can be further defined as "exacerbation with respiratory failure".

Figure 1 depicts a flow diagram describing a suggested clinical approach to suspected COPD exacerbations. The necessary investigations needed to confirm a diagnosis of COPD exacerbation, as well as investigations needed to rule out alternative diagnoses are provided.

Although our proposed definition for COPD exacerbation appears to be more specific than what currently exists, this proposed definition for AECOPD and our proposed approach to diagnosis of AECOPD would need to be validated in prospective clinical studies.

Conclusions:

A more accurate definition is critical to obtaining a better understanding on diagnosis and treatment as well as the true prevalence of COPD exacerbations. Our current definitions of AECOPD are imperfect and not specific. A wide variety of potential medical conditions, such as congestive heart failure, anemia, or pulmonary embolism, can cause increased respiratory symptoms and dyspnea in a patient with COPD. Any of these conditions can potentially and mistakenly meet our current definitions of 'COPD exacerbation'. Currently, in the absence of a single biomarker to easily identify a COPD exacerbation in clinical practice, it seems likely that an improved definition of AECOPD will incorporate a combination of: 1) clinical symptoms such as worsening dyspnea, cough and/or sputum; 2) positive laboratory biomarkers suggesting AECOPD such as serum CRP and serum neutrophilia or eosinophilia, and 3) exclusion of other potential etiologies via negative chest radiograph and negative laboratory tests for cardiac, pulmonary or hematologic disorders that can mimic AECOPD. Future research will hopefully elucidate better biomarkers that are both sensitive and highly specific for AECOPD and will ultimately lead to greater diagnostic accuracy for these potentially devastating events that shape the natural history of COPD.

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Figure Legend:

Figure 1:

A suggested clinical approach to suspected COPD exacerbations.

Confirmation of COPD exacerbation requires: 1) Symptoms compatible with COPD exacerbation; 2) A patient history of COPD or risk factors for COPD; 3) Laboratory investigations compatible with COPD exacerbation; and 4) Laboratory investigations that rule out other diagnoses.

Patient presenting with acute **worsening of dyspnea** which may also be accompanied by increases in:

- **Cough** and/or
- **Sputum purulence** and/or
- **Sputum volume**

Identify Risk Factors for COPD:

- Known history of COPD
- ≥ 10 pack year smoking history or second-hand smoke exposure
- History of exposure to fumes or occupational dusts

Assess for COPD Exacerbation

Rule out alternative diagnoses

Perform a history and physical exam.

Then complete workup to determine if patient fulfills necessary criteria for COPD Exacerbation:

1) Assess dyspnea: VAS ≥ 5 on an analogue visual score that ranges from 0 to 10)

2) Assess oxygen saturation:
O2 desaturation ≤ 4% below that of stable state, or O2 saturation ≤ 90% on room air if no baseline value available

3) Do bloodwork:
CRP ≥ 3 mg/L **and**
Circulating blood neutrophils ≥ 9000 cells/mm^3 or circulating blood eosinophils ≥ 2%

1) Obtain chest xray:
Rule out pneumonia, congestive heart failure, or pneumothorax/pleural effusion

2) Consider D dimer if pulmonary embolism is suspected. If D dimer is positive and pulmonary embolism is suspected then proceed to CT- Angiography

3) Consider ordering ECG and blood for troponins and BNP if cardiac ischemia or CHF is suspected

If patient meets the 3 criteria above for COPD exacerbation and alternative diagnoses are ruled out then treat for COPD exacerbation.

If alternative diagnosis is established, then treat for alternative diagnosis and re-assess patient's status after several days.

Table 1. Potential New Exacerbation Definition (analogous to events in coronary artery disease). (Adapted

from references 65 and 66)

Coronary Artery Disease	COPD

Myocardial Infarction (heart attack)
 	
   Chest pain
 	
   Abnormal ECG
 	
   Elevated troponin
	COPD Exacerbation (lung attack)
	
	   Increased Dyspnea (VAS ≥ 5 on an analogue visual score that ranges from 0 to 10)
	
	and
	
	   O_2 desaturation ≤ 4% below that of stable state, or O2 saturation ≤ 90% if no baseline value available
	
	and
	
	   CRP ≥ 3 mg/L
	
	and
	
	   Circulating blood neutrophils ≥ 9000 cells/mm or circulating blood eosinophils ≥ 2%
	
	and
	
	   No pneumonia or congestive heart failure or pneumothorax or pleural effusion on chest radiograph

Cardiogenic Shock
 	
   Same syndrome, plus shock
	Respiratory Failure
	
	   Same syndrome, plus PaCO2 > 45 mm Hg

VAS: visual analogue scale (0-10); CRP: C-reactive protein; WBC: white blood cell, PaCO2: partial pressure of

carbon dioxide in arterial blood.

Table 2.

Causes of exacerbations or exacerbation-like symptoms in COPD

Etiology	Estimated percent
Viral infection	30-60
Bacterial infection	30-50
Eosinophilic inflammation	20
Pulmonary embolism	3
Pneumonia	6-8
Congestive heart failure	6-8
Poor medication adherence	5