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Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis, and staging

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INTRODUCTION — Chronic obstructive pulmonary disease (COPD) has an extensive, adverse effect on both patients and the healthcare system.

- With respect to patients, COPD causes physical impairment, debility, reduced quality of life, and death. It is the fourth-ranked cause of death in the United States, killing more than 120,000 individuals each year.
- With respect to the healthcare system, COPD causes high resource utilization, which includes frequent clinician office visits, frequent hospitalizations due to acute exacerbations, and chronic therapy (eg, long-term oxygen therapy, medication). This is a consequence of the high prevalence and chronicity of COPD [1].

It is important to recognize and diagnose COPD early because appropriate management can prevent and decrease symptoms (especially dyspnea), reduce the frequency and severity of exacerbations, improve health status, improve exercise capacity, and prolong survival. Despite this, COPD is underdiagnosed [2]. Only 15 to 20 percent of smokers are ever diagnosed with COPD, although the majority develop airflow obstruction [3].

The definition, clinical manifestations, diagnostic evaluation, and staging of COPD are discussed in this topic review. The natural history, prognosis, and treatment of COPD are discussed separately. (See "Natural history and prognosis of COPD" and "Management of stable chronic obstructive pulmonary disease" and "Management of acute exacerbations of chronic obstructive pulmonary disease".)

DEFINITION — It is important to understand the difference between the definition of a disease and its diagnostic criteria [4]. The definition of a disease is the description of the clinical features that distinguish individuals who have the disease from those who do not. In contrast, diagnostic criteria are clinical features of a disease that have been proven to distinguish the disease from other diseases that manifest similarly.

Clinical features used to define a disease are often part of the diagnostic criteria for the disease; however, the diagnostic criteria may include clinical features that are not part of the definition. Diagnostic criteria are much more important than definitions in both clinical

practice and research [5,6]. This section provides the definition of COPD. Diagnostic criteria are described below. (See 'Diagnosis' below.)

The American Thoracic Society, European Respiratory Society, and the British Thoracic Society have each defined COPD using slightly different wording and approaches over the past 15 years [4]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) — a report produced by the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO) — defines COPD as follows [5]:

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases."

Types of COPD — Earlier definitions have distinguished different types of COPD (ie, emphysema, chronic bronchitis, asthma), a distinction that is not included in the GOLD definition [6-8].

- Chronic bronchitis is defined by a chronic productive cough for three months in each of two successive years in a patient in whom other causes of chronic cough have been excluded [9]. This definition has been used in many studies, despite the arbitrarily selected symptom duration and lack of biologic rationale.
- Emphysema is defined by abnormal and permanent enlargement of the airspaces that are distal to the terminal bronchioles. This is accompanied by destruction of the airspace walls, without obvious fibrosis (ie, there is no fibrosis visible to the naked eye) [10]. Exclusion of obvious fibrosis was intended to distinguish the alveolar destruction due to emphysema from that due to the interstitial pneumonias. However, many studies have found increased collagen in the lungs of patients with mild COPD, indicating that fibrosis exists [11,12]. Emphysema can exist in individuals who do not have airflow obstruction; however, it is more common among patients who have moderate or severe airflow obstruction [5].
- Asthma is "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variably, airflow obstruction within the lung that is often reversible either spontaneously or with treatment" [13].

The following observations are consistent with the notion that different types of COPD exist:

- The bronchial inflammation of asthma is different from that of chronic bronchitis or emphysema (figure 1) [14-16]. Asthma is associated with CD4+ T-lymphocytes, eosinophils, and increased interleukin (IL)-4 and IL-5. In contrast, chronic bronchitis and emphysema are associated with CD8+ T-lymphocytes, neutrophils, and CD68+ monocytes/macrophages (picture 1) [17-21].

- Asthma affects patients of all ages and has a low mortality to prevalence ratio. In contrast, chronic bronchitis and emphysema typically manifest in the sixth decade of life and have a higher mortality to prevalence ratio.

Interrelationships — There is substantial overlap among the types of COPD, as illustrated in the figure (figure 2). Important points about their interrelationship include:

- Patients with asthma whose airflow obstruction is completely reversible are not considered to have COPD (subset nine in the figure).
- Patients with asthma whose airflow obstruction does not remit completely are considered to have COPD (subsets six, seven, and eight in the figure). The etiology and pathogenesis of the COPD in such patients may be different from that of patients with chronic bronchitis or emphysema.
- Chronic bronchitis and emphysema with airflow obstruction commonly occur together (subset five in the figure) [22]. Some of these patients may also have asthma (subset eight in the figure).
- Individuals with asthma may develop a chronic productive cough, either spontaneously or due to exposure (eg, cigarette smoke). Such patients are often referred to as having asthmatic bronchitis, although this terminology has not been officially endorsed in clinical practice guidelines (subset six in the figure).
- Persons with chronic bronchitis, emphysema, or both are not considered to have COPD unless they have airflow obstruction (subsets one, two, and eleven in the figure) [23,24].
- Patients with airflow obstruction due to diseases that have a known etiology or a specific pathology (eg, cystic fibrosis, bronchiectasis, obliterative bronchiolitis) are not considered to have COPD (subset 10 in the figure). However, these exclusions are loosely defined [25].

Consistent with the idea that significant overlap exists among the different types of COPD, many individuals have bronchial inflammation with features of both asthma and chronic bronchitis/emphysema [16]. Similarly, the nature of the bronchial inflammation varies widely even among individuals with a single type of COPD. A number of initiatives are in progress to provide rigorous phenotyping of COPD patients in order to define more homogeneous groups.

CLINICAL FEATURES

History — There are three typical ways in which patients with COPD present. Some patients have few complaints, but an extremely sedentary lifestyle [26]. Other patients describe chronic respiratory symptoms (eg, dyspnea on exertion, cough). Finally, some patients present with an acute exacerbation (eg, wheezing, cough, dyspnea) (table 1A-B).

- Patients who have an extremely sedentary lifestyle but few complaints require careful interrogation to elicit a history that is suggestive of COPD. This presentation is the result of patients unknowingly avoiding exertional dyspnea (the most common early symptom of COPD) by shifting their expectations and limiting their

activity. They may be unaware of the extent of their limitations or that their limitations are due to respiratory symptoms, although they may complain of fatigue.

- Patients who present with respiratory symptoms generally complain of dyspnea and chronic cough. The dyspnea may initially be noticed only during exertion. However, it eventually becomes noticeable with progressively less exertion or even at rest. The chronic cough is characterized by the insidious onset of sputum production, which occurs in the morning initially, but may progress to occur throughout the day. The daily volume rarely exceeds 60 mL. The sputum is usually mucoid, but becomes purulent during exacerbations.
- Patients who present with an acute chest illness report increased cough, purulent sputum, wheezing, and dyspnea that occur intermittently, with or without fever. Diagnosis can be problematic in such patients. The complaint of wheezing plus dyspnea often leads to an incorrect diagnosis of asthma. Conversely, other illnesses with similar manifestations are often incorrectly diagnosed as a COPD exacerbation (eg, heart failure, bronchiectasis, bronchiolitis) (table 2). The interval between exacerbations decreases as the severity of the COPD increases.

Most patients with COPD have a history of cigarette smoking or alternative inhalational exposure [27]. However, some patients develop COPD without an obvious risk factor. Approximately 20 percent of patients who have COPD (defined by lung function alone) and 20 percent of patients who die from COPD are lifelong nonsmokers [28,29]. (See "Chronic obstructive pulmonary disease: Risk factors and risk reduction".)

Other historical features that should increase suspicion for COPD include hemoptysis, and certain comorbidities (eg, lung cancer, coronary artery disease, osteoporosis, depression, skeletal muscle weakness) [30-35]. Weight loss can also occur in COPD and is associated with a worse prognosis. However, the majority of COPD patients, at present, are overweight or obese.

Physical examination — The physical examination of the chest varies with the severity of the COPD (table 1A-B).

- Early in the disease, the physical examination may be normal, or may show only prolonged expiration and wheezes on forced exhalation.
- As the severity of the airway obstruction increases, physical examination may reveal hyperinflation, decreased breath sounds, wheezes, crackles at the lung bases, and/or distant heart sounds [36]. In addition, the diaphragm may be depressed and limited in its motion, and the anteroposterior diameter of the chest may be increased. These findings are usually features of relatively severe disease.
- Patients with end-stage COPD may adopt positions that relieve dyspnea, such as leaning forward with arms outstretched and weight supported on the palms. Other physical examination findings include full use of the accessory respiratory muscles of the neck and shoulder girdle, expiration through pursed lips, paradoxical retraction of the lower interspaces during inspiration (ie, Hoover's sign), cyanosis, asterixis due to severe hypercapnia, and an enlarged, tender liver due to right heart failure. Neck vein distention may also be observed because of increased intrathoracic pressure, especially during expiration.

Pulmonary function tests — Pulmonary function tests are the cornerstone of the diagnostic evaluation of patients with suspected COPD. They are discussed in this context below. (See 'Diagnosis' below and "Office spirometry".)

Imaging — Chest radiography and computed tomography are imaging studies that are commonly performed in patients with COPD; however, neither is required to diagnose COPD. (See 'Diagnosis' below.)

Chest radiography — Plain chest radiographs have poor sensitivity for detecting COPD. As an example, only about half of patients with COPD of moderate severity are identified as having COPD by a plain chest radiograph (ie, sensitivity of 50 percent). Radiographic features suggestive of COPD (usually advanced disease) include:

- Rapidly tapering vascular shadows, increased radiolucency of the lung, a flat diaphragm, and a long, narrow heart shadow on a frontal radiograph, accompanied by a flat diaphragmatic contour and an increased retrosternal airspace on a lateral radiograph. These findings are due to hyperinflation.
- Bullae, defined as radiolucent areas larger than one centimeter in diameter and surrounded by arcuate hairline shadows. They are due to locally severe disease, and may or may not be accompanied by widespread emphysema.
- Prominent hilar vascular shadows and encroachment of the heart shadow on the retrosternal space [37]. The cardiac enlargement may become evident only on comparison with previous chest radiographs. These findings are due to pulmonary hypertension and cor pulmonale, which can be secondary to COPD. (See "Overview of pulmonary hypertension".)

Computed tomography — Computed tomography (CT) has greater sensitivity and specificity than standard chest radiography for the detection of emphysema, but not chronic bronchitis or asthma. This is particularly true with high resolution CT (ie, collimation of 1 to 2 mm) [38-40]. (See "High resolution computed tomography of the lungs".)

CT can determine whether the emphysema is centriacinar or panacinar. Centriacinar emphysema occurs preferentially in the upper lobes and produces holes in the center of secondary pulmonary lobules (picture 2). In contrast, panacinar emphysema more commonly involves the lung bases and involves the entire secondary pulmonary lobule (picture 3). Panacinar emphysema can cause a generalized paucity of vascular structures.

Newer CT scanners with higher resolution and new analytical methods can resolve airway dimensions, although the clinical significance of these measures is undefined [41,42]. CT plays an important role in evaluating emphysematous patients for lung volume reduction surgery. (See "Lung volume reduction surgery in COPD".)

Arterial blood gases — Arterial blood gases reveal mild or moderate hypoxemia without hypercapnia in patients with mild COPD. As the disease progresses, the hypoxemia becomes more severe and hypercapnia develops. Hypercapnia occurs with increasing frequency as the forced expiratory volume in one second (FEV1) falls below one liter.

Blood gas abnormalities worsen during acute exacerbations and may also worsen during exercise and sleep.

DIAGNOSIS — The diagnosis of COPD should be suspected in all patients who report any combination of the following: chronic cough, chronic sputum production, dyspnea at rest or with exertion, or a history of inhalational exposure to tobacco smoke, occupational dust, or occupational chemicals (table 3) [5,9]. Dyspnea with exertion may be underappreciated by individuals who unknowingly restrict their activity level. COPD is typically slowly progressive, persistent, and exacerbated by respiratory infection.

Those patients who have the features described above should undergo pulmonary function testing (PFTs), especially if there is a history of exposure to triggers of COPD (eg, tobacco smoke, occupational dust) [43]. PFTs are used to diagnose COPD, determine the severity of the airflow obstruction, and follow disease progression.

The most important values measured are the forced expiratory volume in one second (FEV1) and the forced vital capacity (FVC). The forced expiratory volume in six seconds (FEV6) is sometimes used as an approximation for the FVC [44-47]. An FEV1/FVC ratio less than 0.70 generally indicates airway obstruction. The interpretation of spirometry is discussed separately. (See "Office spirometry", section on 'Interpretation'.)

COPD is confirmed when a patient, who has symptoms that are compatible with COPD, is found to have airflow obstruction (FEV1/FVC ratio less than 0.70 and an FEV1 less than 80 percent of predicted) and there is no alternative explanation for the symptoms and airflow obstruction (eg, bronchiectasis, vocal cord paralysis, tracheal stenosis).

The lower limit of normal of the FEV1/FVC ratio has been advocated as an alternative to the absolute value of an FEV1/FVC < 0.70, the usual diagnostic criterion for airflow limitation [9,48]. Use of the lower limit of normal for FEV1/FVC may be particularly important in patients over the age of 60, as the FEV1/FVC ratio normally decreases with age. Using an absolute value for the FEV1/FVC can lead to a false diagnosis of COPD in some elderly patients. (See "Management of stable chronic obstructive pulmonary disease".)

The FEV1 and FVC are not the only values derived from PFTs. Decreased inspiratory capacity and vital capacity, accompanied by increased total lung capacity, functional residual capacity, and residual volume are indicative of hyperinflation. The single breath carbon monoxide diffusing capacity (DLCO) decreases in proportion to the severity of emphysema; however, it can not be used to detect mild emphysema because it is neither a sensitive nor a specific test. (See "Dynamic hyperinflation in patients with COPD".)

SCREENING — Routine screening spirometry is generally not indicated for adults who have none of the features suggestive of COPD (eg, no dyspnea, cough, sputum production, or history of tobacco smoke exposure), as asymptomatic mild airflow obstruction does not require treatment [49,50]. Asymptomatic and nonsmoking subjects with mild airflow obstruction, but no history of asthma, do not have the same progressive decline in lung function that is observed among individuals who have a similar degree of airflow

obstruction and are symptomatic or continue to smoke [51]. On the other hand, as many as 20 percent of individuals with severe airway obstruction due to smoking or asthma will not report symptoms. However, decrements in FEV1, even within the normal range, are associated with increased risk of acute cardiac events independent of age, gender, and smoking history [30]. Thus, judgment is needed to assess which patients would benefit from measurement of PFTs as the diagnosis of COPD may alter management of other concurrent conditions and may affect the approach to exercise.

STAGING — The FEV1 (expressed as a percentage of predicted) is often used to stage disease severity [52]. The FEV1/FVC ratio is not used for this purpose because measurement of FVC becomes less reliable as the disease progresses (the long exhalations are difficult for the patients).

Different clinical practice guidelines use different cut-off values, but most are similar to the GOLD staging system (table 4) [5].

The GOLD staging system has been criticized for underestimating the importance of the extrapulmonary manifestations of COPD in predicting outcome. The BODE index addresses this criticism (table 5). The four factors included in the BODE index are weight (BMI), airway obstruction (FEV1), dyspnea (Medical Research Council dyspnea score), and exercise capacity (six-minute walk distance) (calculator 1). This index provides better prognostic information than the FEV1 alone and can be used to assess therapeutic response [53-56].

A component of disease assessment that is used in research studies is to evaluate the impact of airflow limitation on quality of life. The St. George's Respiratory Questionnaire (SGRQ) is a 76 item questionnaire that includes three component scores (ie, symptoms, activity, and impact on daily life) and a total score. It has been validated in patients with COPD, asthma, and bronchiectasis [52,57,58].

INFORMATION FOR PATIENTS — Educational materials related to COPD are available for patients. (See "Patient information: Chronic obstructive pulmonary disease (COPD, including emphysema)" and "Patient information: Chronic obstructive pulmonary disease (COPD) treatments".) We encourage you to print or e-mail these topic reviews, or to refer patients to our public web site, www.uptodate.com/patients, which includes these and other topics.

SUMMARY AND RECOMMENDATIONS

- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) says: "Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases." (see 'Definition' above).

- Earlier definitions have distinguished different types of COPD: emphysema, chronic bronchitis, and asthma. There is substantial overlap among the types of COPD, as illustrated in the figure (figure 2). (See 'Types of COPD' above.)
- There are three typical ways that patients with COPD present. Some patients have few complaints, but an extremely sedentary lifestyle. Other patients describe chronic respiratory symptoms (eg, dyspnea on exertion, cough). Finally, some patients present with an acute exacerbation (eg, wheezing, cough, dyspnea). The physical examination of the chest varies with the severity of the COPD (table 1A-B). (See 'Clinical features' above.)
- The diagnosis of COPD should be considered and pulmonary function tests (PFTs) performed in all patients who report any combination of the following: chronic cough, chronic sputum production, dyspnea, or inhalational exposure to tobacco smoke, occupational dust, or occupational chemicals (table 3). COPD is confirmed when a patient who has symptoms that are compatible with COPD is found to have airflow obstruction (ie, a forced expiratory volume in one second [FEV1]/forced vital capacity [FVC] ratio less than 0.70) and there is no alternative explanation for the symptoms and airflow obstruction. (See 'Diagnosis' above.)
- The GOLD staging system is shown in the table (table 4). Although well recognized and commonly used, the GOLD staging system has been criticized for underestimating the importance of the extrapulmonary manifestations of COPD in predicting outcome. The BODE index addresses this criticism (table 5). (See 'Staging' above.)

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Management of stable chronic obstructive pulmonary disease

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INTRODUCTION — Chronic obstructive pulmonary disease (COPD) is a common condition with a high and continually increasing mortality, affecting men and women equally. It is estimated that approximately 8 percent of all individuals have COPD, including approximately 10 percent of individuals older than 40 years [1]. The true prevalence is likely higher because COPD is both under-recognized and under-diagnosed. COPD was the sixth leading cause of death worldwide in 1990 and is expected to become the third leading cause of death by 2020 [2].

The management of stable COPD will be reviewed here. The diagnosis, natural history, and prognosis of COPD, risk factors for COPD, and treatment of acute exacerbations are discussed separately. (See "Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis, and staging" and "Natural history and prognosis of COPD" and "Chronic obstructive pulmonary disease: Risk factors and risk reduction" and "Management of acute exacerbations of chronic obstructive pulmonary disease".)

GENERAL APPROACH — Pharmacotherapy for COPD is used to prevent and decrease symptoms (especially dyspnea), reduce the frequency and severity of exacerbations, improve health status, and improve exercise capacity [3]. We share the philosophy of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) that pharmacologic and nonpharmacologic therapies should be added in a stepwise fashion to control symptoms, decrease exacerbations, and improve patient function and quality of life. In the discussion that follows, the various therapies for COPD and clinical evidence for each is reviewed. Finally, an approach to the management of patients with stable COPD is outlined. (See 'Summary and recommendations' below.)

The mainstays of drug therapy of stable COPD are bronchodilators, primarily beta agonists and anticholinergics, and inhaled glucocorticoids, given alone or in combination depending upon the severity of disease and response to therapy (table 1 and table 2). These are generally administered via metered dose or dry powder inhalers. The bronchodilator theophylline, which is only modestly effective and has more side effects than other bronchodilators, is occasionally used for patients with refractory COPD.

Education about the purpose and dosing of medications, timing of short-acting bronchodilators prior to exertion, and proper inhaler technique is essential. (See "Delivery of inhaled medication in adults" and "The use of inhaler devices in adults" and "Patient information: Asthma inhaler techniques in adults".)

Some regimens used in the past are now rarely used. These include systemic glucocorticoids, mucoactive agents, and chronic antibiotic therapy. (See 'Rarely used medications' below.)

Supplemental therapies, such as oxygen, pulmonary rehabilitation, and smoking cessation also play an important role in the management of COPD. (See 'Supplemental therapy' below.)

In order to determine whether the patient has achieved an adequate response to therapy, it is necessary to monitor symptoms (eg, dyspnea, exercise tolerance, cough, sputum production), airflow (ie, spirometry), the amount of as-needed medication use, and the frequency of exacerbations.

ASSESSING DISEASE SEVERITY — A staging system for COPD severity has been established by The Global Initiative for Chronic Obstructive Lung Disease (GOLD), which defines disease severity according to airflow limitation, based on forced expiratory volume in one second (FEV1) and the ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FEV1/FVC) (table 1) [3]. This staging system is also used as a guide for the management of patients with stable COPD (table 2). (See "Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis, and staging", section on 'Staging'.)

The multidimensional BODE index may be used to assess an individual's risk of death or hospitalization due to COPD (calculator 1); however, it is not used to guide therapy. (See "Natural history and prognosis of COPD", section on 'BODE index'.)

BRONCHODILATORS — Bronchodilators are the therapeutic mainstay for patients with COPD. They include beta agonists, anticholinergics, and theophylline, which is used less often. Bronchodilators have been consistently shown to induce long-term improvements in symptoms, exercise capacity, and airflow limitation, even when there is no spirometric improvement following a single test dose [4-7].

Beta agonists and anticholinergics are available in short-acting and long-acting inhaled formulations. All symptomatic patients with COPD should be prescribed a short-acting bronchodilator to be used on an as-needed basis [3]. A regularly scheduled long-acting bronchodilator should be added if symptoms are inadequately controlled with short-acting bronchodilator therapy.

Most bronchodilators can be administered by inhalation, orally, subcutaneously, or intravenously. For COPD patients, inhalation is the recommended delivery method because it maximizes the bronchodilator's direct effect on the airways, while minimizing systemic effects. A metered dose inhaler (MDI), dry powder inhaler (DPI), or nebulizer can be used to deliver a bronchodilator medication by inhalation. MDIs (and DPIs) simplify therapy, improve compliance, and may reduce extra medication usage and patient cost. When used correctly, they achieve a bronchodilator response equivalent to that achieved with a nebulizer. However, for some patients, a nebulizer may be easier to use and may be necessary when proper MDI technique is not possible. (See "Delivery of inhaled

medication in adults" and "The use of inhaler devices in adults" and "Patient information: Asthma inhaler techniques in adults".)

Short-acting bronchodilators — The first decision that most clinicians face when managing a patient with COPD is which short-acting bronchodilator is most appropriate when mild intermittent symptoms begin. Short-acting beta agonists and anticholinergics can be used alone or in combination. All of the short-acting bronchodilators improve lung function and symptoms. The unique advantage of short-acting beta agonists is their rapid onset of action.

Combination therapy is generally preferred at this stage because this provides the patient with advantages unique to each medication. In addition, the combination of a short-acting beta agonist plus a short-acting anticholinergic achieves a greater bronchodilator response than either one alone [8]. However, monotherapy with either agent is acceptable.

Beta agonists — Short-acting beta agonists include albuterol, levalbuterol, and pirbuterol. They have been proven in randomized, controlled trials and meta-analyses to improve symptoms and lung function [9].

Use of short-acting beta agonists on an as-needed basis decreases sympathomimetic exposure without significant reduction of benefit. A trial randomly assigned 53 patients with COPD to receive regularly scheduled albuterol or placebo, while continuing a medication regimen that consisted of ipratropium bromide, inhaled glucocorticoid, and as-needed albuterol [10]. Regularly scheduled albuterol increased the total amount of albuterol received two-fold, without a clinically significant impact on lung function, symptoms, or exercise capacity.

Most controlled trials that have compared as-needed versus regularly scheduled dosing have used a similar trial design. Specifically, they compared patients who received regularly scheduled plus as-needed short-acting beta agonist, versus patients who received placebo plus as-needed short-acting beta agonist. This trial design is necessary to alleviate the practical and ethical concerns about having a group without access to short-acting beta agonist for rescue from acute dyspnea.

Most recommended doses of beta agonists (both short-acting and long-acting) result in less than maximal bronchodilation. Risks of overuse are possible if an individual attempts to achieve maximal bronchodilation by using higher doses. These risks include tremor and reflex tachycardia due, in part, to peripheral arterial dilation. Hypokalemia can also occur in extreme cases and should be monitored in patients at risk. Oral beta-2 agonists are generally not prescribed because their incidence of side effects is particularly high. (See "Sympathetic activity and potassium balance" and "Management of the patient with severe COPD and coronary artery disease" and "Arrhythmias in COPD".)

Anticholinergics — Short-acting anticholinergic medications improve lung function and symptoms. As an example, one double-blind trial randomly assigned 183 patients with moderate to severe COPD to receive ipratropium alone (80 mcg, three times per day), formoterol, or placebo for 12 weeks [11]. Short-acting beta agonists were permitted as-needed for relief of acute dyspnea. Compared to placebo, ipratropium improved lung

function, increased exercise capacity, decreased dyspnea, and decreased cough. As-needed and regularly scheduled dosing regimens of short-acting anticholinergics have not been compared. (See "Role of anticholinergic therapy in COPD".)

Comparison — Albuterol and ipratropium have been compared in randomized, controlled trials [8,12,13]. On average, both medications improve lung function to a similar degree. Side effects are unique to each medication class, but are minimal at commonly prescribed doses.

Combination therapy — The degree of bronchodilation achieved by short-acting beta agonists and anticholinergics is additive, especially when typically recommended (submaximal) doses of each agent are combined [3,8,13]. As an example, the largest trial randomly assigned 534 patients with COPD to receive albuterol alone, ipratropium alone, or combination therapy (albuterol plus ipratropium) [8]. Combination therapy increased the mean peak FEV1 more than either agent alone, but did not alter the frequency of exacerbations. A similar study reported that combination therapy decreased the frequency of exacerbation compared to albuterol, but not ipratropium [13].

Long-acting bronchodilators — Short-acting bronchodilators alone or in combination may be insufficient to control symptoms. A regularly scheduled long-acting inhaled bronchodilator (LABA) is added in these patients, who have more advanced disease in the range of GOLD stage II and higher (table 1 and table 2) [3]. Either a long-acting beta agonist or a long-acting anticholinergic is acceptable. In general, a long-acting anticholinergic is preferred over a long-acting beta agonist because most of the effects of the currently available once daily anticholinergic appear to be superior to the twice daily beta agonists that are available for use.

Theophylline is another option, although least preferred, because its effects are modest and toxicity is a concern. The use of theophylline is usually limited to an add-on therapy when symptoms continue in patients with more severe disease despite the use of other treatments. (See 'Theophylline' below.)

Beta agonists — The long-acting beta agonists (LABAs) include salmeterol, formoterol, and arformoterol. Multiple studies have demonstrated their benefit in patients with stable COPD [5,14-20]. The largest trial of salmeterol, Toward a Revolution in COPD Health (TORCH), randomly assigned 6112 patients with mostly severe COPD (mean FEV1 44 percent of predicted, (table 1) to one of four treatment arms for three years: salmeterol alone (50 mcg twice daily), fluticasone alone (500 mcg twice daily), combination therapy (salmeterol plus fluticasone), or placebo [17]. Salmeterol significantly decreased exacerbation rates, improved lung function, and improved health-related quality of life compared to placebo. There was a trend toward a decrease in mortality (13.5 versus 15.2 percent), although this reduction did not achieve statistical significance.

The true decrease in mortality in TORCH may be larger than the apparent difference noted above because of methodologic issues common to intention-to-treat trials, especially those providing medications with symptomatic relief. The placebo arm had a high discontinuation rate (44 percent) and lower than expected mortality. This may have occurred because the

sickest patients treated with placebo had greater symptoms and left the trial to take therapy [21]. In such a situation, the intention to treat analysis would be expected to underestimate the real benefit of active therapy.

Anticholinergic — The long-acting anticholinergic medication, tiotropium, improves lung function and decreases dynamic hyperinflation, while also decreasing dyspnea and exacerbations [16,22-27]. In addition, it improves trough airflow (ie, 24 hours after the last dose) and reduces hyperinflation, indicating that its effects are long-lasting [28]. Tiotropium may slow the rate of decline in FEV1 [28-31]. (See "Role of anticholinergic therapy in COPD", section on 'Tiotropium'.)

Conflicting evidence has been reported regarding possible adverse cardiovascular effects of anticholinergic therapy in patients with COPD; however, data from a long-term, randomized trial (Understanding Potential Long-Term Impacts on Function with Tiotropium [UPLIFT]) support the safety of tiotropium [32]. This is discussed in greater detail separately. (See "Role of anticholinergic therapy in COPD", section on 'Potential risks'.)

Comparison — Salmeterol and tiotropium have been compared in randomized, controlled trials [25,26]. Tiotropium induced greater improvement of lung function in both trials and greater improvement of symptoms in one of the trials. In addition, there were fewer deaths and exacerbations in the tiotropium group in both trials, although the differences were not statistically significant. Neither trial was sufficiently powered to detect statistically significant differences in these outcomes.

Both salmeterol alone and tiotropium alone have been compared to the combination of a long-acting bronchodilator plus a glucocorticoid. (See 'Bronchodilators plus inhaled glucocorticoids' below.)

Combined therapy — In patients with GOLD stage II-IV COPD whose symptoms are not well-controlled with a single long-acting bronchodilator, the combination of both an anticholinergic and a beta-agonist long-acting bronchodilator may provide better symptom relief (table 2). However, data from controlled trials are conflicting. As an example, the long-acting anticholinergic agent tiotropium plus a long-acting inhaled beta agonist has been compared to tiotropium alone:

- One trial randomly assigned 449 patients with moderate or severe COPD to receive tiotropium plus placebo, tiotropium plus salmeterol, or tiotropium plus both salmeterol and fluticasone for one year [33]. When tiotropium plus salmeterol was compared to tiotropium alone, there were no significant differences in the primary end point of the proportion of patients who had exacerbations that required systemic glucocorticoids or antibiotics (64.8 and 60.0 with double and triple therapy versus 62.8 percent with tiotropium alone) or in lung function or the number of hospitalizations. However, the trial was limited by premature cessation of therapy in over 40 percent of patients and crossovers to additional open-label therapies.

The efficacy of triple inhaler therapy with tiotropium plus both salmeterol and fluticasone is discussed below. (See 'Refractory disease' below.)

- A smaller randomized, crossover trial compared tiotropium plus formoterol versus tiotropium alone [34]. The tiotropium plus formoterol group had greater improvement in lung function and required rescue short-acting beta agonist less often.

Minimal data are available comparing the combination of tiotropium plus a long-acting beta agonist (LABA) with the combination of a LABA plus inhaled glucocorticoid. (See 'Bronchodilators plus inhaled glucocorticoids' below.) A comparison of tiotropium plus salmeterol versus salmeterol alone has not been reported.

INHALED GLUCOCORTICOIDS — COPD is characterized by both airway and systemic inflammation [35]. Inhaled glucocorticoids (also known as inhaled corticosteroids or ICS) may reduce this inflammation [36-41]. The available data, which are presented in detail elsewhere, suggest that inhaled glucocorticoids decrease exacerbations and modestly slow the progression of respiratory symptoms, but appear to have little impact on lung function and mortality. In COPD, inhaled glucocorticoids are used as part of a combined regimen, but should NOT be used as sole therapy for COPD (ie, without long-acting bronchodilators). (See "Role of inhaled glucocorticoid therapy in stable COPD".)

Adverse effects associated with inhaled glucocorticoids are discussed separately. (See "Major side effects of inhaled glucocorticoids".)

BRONCHODILATORS PLUS INHALED GLUCOCORTICOIDS — Inhaled glucocorticoids are typically used in combination with a long-acting bronchodilator for patients in GOLD stage III-IV, who have significant symptoms or repeated exacerbations, despite an optimal bronchodilator regimen (table 2). The addition of an inhaled glucocorticoid may be warranted earlier (ie, at the same time that the long-acting inhaled bronchodilator is initiated) if there are signs of inflammation or an asthmatic component to the COPD [42]. Inhaled glucocorticoids are continued in patients whose symptoms, frequency of exacerbations, and/or lung function improve within one month.

Combination therapy significantly improves some outcomes compared to placebo, long-acting beta agonists alone, inhaled glucocorticoids alone, or long-acting anticholinergics alone [17,43-46]. Support for these conclusions comes from the two largest trials of combination therapy [17,45]. In the TORCH trial described above (6112 patients with moderate to severe COPD), salmeterol plus fluticasone significantly improved the secondary end points of lung function, health status, and the rate of exacerbations compared to placebo, salmeterol alone, or fluticasone alone [17]. Estimates of cost-effectiveness also favored the salmeterol-fluticasone combination over placebo or either of the individual agents [47]. (See 'Long-acting bronchodilators' above.)

With respect to the primary end point of the TORCH trial, a reduction in mortality rate over three years, salmeterol plus fluticasone minimally decreased mortality compared to placebo (10.3 versus 12.6 percent, hazard ratio 0.81, 95% CI, 0.67-0.98). While this is only of

borderline statistical significance, the actual effect on mortality may be larger than reported; in the intention to treat analysis sicker patients in the placebo group may have left the trial, seeking active treatment. The risk of death in the combination group did not differ from that in the salmeterol alone group (hazard ratio 0.95), but was significantly lower than the fluticasone alone group (hazard ratio 0.77, 95% CI, 0.64-0.93).

The second large trial of combination therapy included 1323 patients with stable, mostly severe COPD (mean FEV1 39 percent of predicted, (table 1) who were randomly assigned to receive either salmeterol plus fluticasone or tiotropium alone for two years [45]. There was no difference in the frequency of exacerbations, which was the primary endpoint. However, salmeterol plus fluticasone improved several secondary endpoints, including mortality and health status. This trial suggests that there may be a role for initiating regularly scheduled therapy using a long-acting beta agonist plus an inhaled glucocorticoid, instead of a long-acting bronchodilator alone (as recommended in current guidelines). However, these suggestive data are insufficient to warrant routine initiation of such combination therapy [48].

A question that has been less well studied is whether it would be preferable to add a second long-acting bronchodilator (from the alternate class), or an inhaled glucocorticoid in patients whose disease in not well-controlled with a single long-acting bronchodilator. This was addressed in a randomized trial in which 592 patients with moderate to severe COPD were assigned to tiotropium plus formoterol or fluticasone plus salmeterol [49]. After six weeks, lung function was better in the tiotropium-formoterol group as evidenced by an increase in FEV1 of 103 mL. Rescue medication use did not differ significantly between the groups; other important endpoints, including exacerbations and mortality, were not assessed.

The combination of a long-acting anticholinergic plus an inhaled glucocorticoid has not been compared to a long-acting anticholinergic alone.

REFRACTORY DISEASE — Some patients continue to have symptoms or repeated exacerbations of COPD despite therapy with an optimal long-acting inhaled bronchodilator plus an inhaled glucocorticoid (eg, GOLD III or IV) (table 1 and table 2). Evaluating for comorbid conditions that may be contributing to dyspnea (eg, continued smoking, coronary heart disease, heart failure, deconditioning, pulmonary hypertension, thromboembolic disease, respiratory muscle weakness) and poor exercise tolerance may reveal additional therapeutic options.

When managing patients with refractory disease, we assess for exercise-related oxygen desaturation using oximetry during a stair climb or six-minute walk; supplemental oxygen is added, if needed. Other nonpharmacologic therapies, including education about proper inhaler technique and use, pulmonary rehabilitation, and smoking cessation should be part of standard management. (See 'Supplemental therapy' below.)

A small number of carefully selected patients may benefit from surgical intervention. (See 'Surgery' below.)

Triple inhaler therapy — In patients with severe COPD, triple inhaler therapy with a long-acting beta agonist plus an inhaled glucocorticoid plus a long-acting anticholinergic is often used. The validity of this approach is supported by the following studies, although only the first two address the clinically important question of triple versus double therapy, while the other two address the benefit of triple versus single agent therapy:

- The benefits of triple therapy are also suggested by the UPLIFT trial [32]. In this trial, patients were randomized to receive usual COPD care with or without tiotropium; with two-thirds of the patients using an inhaled long acting beta agonist (LABA) and an inhaled glucocorticoid (ICS) as their usual care. The addition of tiotropium to those patients receiving a LABA and an ICS as usual care significantly improved airflows, reduced exacerbations, and improved health related quality of life.
- A retrospective study of 2 cohorts of patients with COPD cared for in the Veterans Affairs (VA) system, compared a regimen of tiotropium plus inhaled LABA plus ICS to a historic, matched COPD population treated with an inhaled LABA plus ICS [50]. The triple combination was associated with a decreased risk of mortality, COPD exacerbations, and hospitalizations. On the other hand, combinations that included tiotropium plus other medications were not associated with these benefits.
- In a double-blind trial, 449 patients with moderate or severe COPD were randomly assigned to one of three treatment groups: tiotropium plus placebo, tiotropium plus salmeterol, or tiotropium plus both salmeterol and fluticasone for one year; the latter two groups were compared with tiotropium alone [33]. Triple therapy, when compared to tiotropium alone, was associated with significant improvements in lung function and disease-specific quality of life and a reduction in all-cause hospitalizations, but not a reduction in overall exacerbation rate.
- In a 12 week randomized trial, 660 subjects with moderate to severe COPD were randomly assigned to a regimen of inhaled budesonide plus formoterol plus tiotropium or to inhaled tiotropium alone [51]. The number of severe exacerbations was significantly lower in the triple therapy group. In addition, statistically significant improvements were noted in prebronchodilator FEV1 and morning symptoms.

Theophylline — In addition to triple inhaler therapy, another option that may be tried is adding a low dose of oral theophylline. Its mechanisms are controversial and numerous, but modest bronchodilation certainly plays a role. A meta-analysis of 20 randomized, controlled trials demonstrated that theophylline improved FEV1, forced vital capacity (FVC), and gas exchange compared to placebo [52]. Improvement in exercise performance depended on the method of testing. Similarly, in a randomized crossover trial of 60 patients with COPD, theophylline decreased dyspnea and improved gas exchange, lung function, and respiratory muscle function [53]. (See "Role of methylxanthines in the treatment of COPD".)

Long-acting extended-release preparations are available. Use of such a preparation at night may reduce nocturnal decrements in respiratory function and morning respiratory symptoms [54].

Theophylline can be toxic. Theophylline is metabolized in the liver and any process that interferes with liver function can rapidly change theophylline levels. In addition, many drugs can interact with theophylline, requiring close monitoring of drug levels and awareness of these issues. In general, patients with COPD can be adequately treated with serum levels in the 8 to 12 mcg/mL range. (See "Theophylline poisoning".)

RARELY USED MEDICATIONS

Systemic glucocorticoids — Systemic glucocorticoids have long been used to treat exacerbations in patients with COPD; however, chronic use can have significant adverse effects and has been associated with an increase in morbidity and mortality [55,56]. The roles of systemic glucocorticoids in the treatment of acute exacerbations of COPD and in chronic stable COPD are discussed in more detail separately. (See "Management of acute exacerbations of chronic obstructive pulmonary disease" and "Role of systemic glucocorticoid therapy in COPD".)

In brief, long-term systemic glucocorticoid therapy is not recommended, even for severe COPD, because of the significant side effects and evidence of increased morbidity and mortality with this therapy [55,56]. In the uncommon circumstance when they are occasionally used, systemic glucocorticoids should be reduced to the lowest dose possible. Also, objective measures of improvement (eg, spirometry, walk test) must be obtained as emotional and euphoric effects of systemic glucocorticoids can cloud a patient's perception of benefit even if no true pulmonary improvement has been obtained [57].

Mucoactive agents — Thick, tenacious secretions can be a major problem in patients with COPD, but there is little evidence that thinning or increasing the clearance of secretions induces clinical improvement. Thus, mucoactive agents are not accepted as routine care for patients with stable COPD. (See "Role of mucoactive agents in the treatment of COPD".)

Oral expectorants (eg, guaifenesin, iodides) offer little benefit to patients with COPD. As an example, one study demonstrated that iodinated glycerol improved cough and chest discomfort in some patients with chronic bronchitis; however dyspnea and lung function were unaltered [58]. This medication is no longer available in the United States.

Acetylcysteine is a mucolytic that purportedly thins the secretions of patients with chronic bronchitis. It has no effect on airflow or sputum volume, and it can induce significant bronchoconstriction when given by inhalation. Studies looking at the value of oral acetylcysteine as an antioxidant therapy for COPD were negative [59]. Alternative mucolytics include dornase alfa (DNase), exogenous surfactant, various proteolytic agents, and various detergents. These agents require additional evaluation prior to their routine use in patients with COPD.

Increasing fluid intake is of no value unless a patient is hypovolemic. Nebulized water or hypertonic saline is without documented benefit and may irritate the airways and induce bronchospasm.

Chronic antibiotic therapy — Chronic antibiotic therapy is generally not indicated for patients with stable COPD (eg, emphysema, chronic bronchitis). However, certain antibiotics, macrolides in particular, may have antiinflammatory effects in addition to their antibiotic effect.

The effect of chronic macrolide therapy on COPD exacerbations was assessed in 109 patients with COPD who were randomly assigned to receive erythromycin 250 mg or placebo twice daily for one year [60]. The erythromycin group had significantly fewer exacerbations than the placebo group. Further studies are needed before considering regular use of chronic macrolide therapy, particularly to assess potential side effects, including selection of resistant organisms.

Patients whose COPD is associated with, bronchiectasis may benefit from chronic antibiotic therapy. The treatment of bronchiectasis is discussed separately. (See "Treatment of bronchiectasis in adults".)

Nonimmunized patients with COPD who are at high risk for contracting influenza and/or have early acute influenza infections may benefit from antiviral therapy. (See "Prevention of seasonal influenza in adults" and "Treatment of seasonal influenza in adults".)

SUPPLEMENTAL THERAPY

Oxygen — Many patients with stable severe COPD (especially GOLD Stage IV disease) have chronic hypoxemia. It is important that this be detected because long-term oxygen therapy improves survival and quality of life in hypoxemic patients with COPD [5,6,61-64]. Improved survival may be due, in part, to improved pulmonary hemodynamics. Improved quality of life is likely due to reduced dyspnea during exercise, which improves performance of activities of daily living.

Long-term oxygen therapy should be prescribed for all patients with COPD who have chronic hypoxemia [65]. The benefits, indications, and prescription of supplemental oxygen are discussed in detail elsewhere. (See "Long-term supplemental oxygen therapy".)

Arterial blood gases and pulse oximetry are the only reliable methods of detecting hypoxemia in patients with COPD because most patients have few if any symptoms that can specifically be related to decreased oxygenation. Arterial blood gas analysis is also helpful in assessing the presence and severity of hypercapnia, which can complicate oxygen therapy. (See "Use of oxygen in patients with hypercapnia".)

Patients can become hypoxemic during airline travel since planes are not always pressurized to sea level. Supplemental oxygen is recommended for individuals whose in-flight PaO2 is expected to fall below 50 mmHg. (See "Traveling with oxygen aboard commercial air carriers" and "Patient information: Supplemental oxygen on commercial airlines".)

Secretion clearance — As discussed above, there is little evidence that routine thinning or increasing the clearance of secretions induces clinical improvement. However, selected patients who have excessive secretions or an ineffective cough may benefit from techniques such as postural drainage, positive expiratory pressure therapy, forced expiratory technique, and flutter valve therapy [66-68].

Smoking cessation — Encouraging smoking cessation is essential because smoking cessation can reduce the rate of FEV1 decline that exists in smokers with COPD. As an example, the Lung Health Study reported a decline in postbronchodilator FEV1 of 54.2 and 66.1 mL in women and men, respectively, who continued to smoke over an 11 year period [69]. Women and men who were sustained quitters of smoking had an FEV1 decline of only 21.5 and 30.2 mL per year, respectively.

Interventions that assist smoking cessation include clinician advice and encouragement, nicotine replacement therapy, bupropion, varenicline, and counseling. The best cessation rates are achieved when counseling is combined with medication therapy. (See "Management of smoking cessation in adults" and "Patient information: Quitting smoking".)

Vaccinations — Infection is a common cause of COPD exacerbation. Vaccinations can prevent some infections and should be offered to patients with stable COPD:

- Pneumococcal polysaccharide vaccine should be offered to patients with COPD who are ≥65 years old, or who are younger than 65 years with a forced expiratory volume in one second (FEV1) less than 40 percent [3]. (See "Pneumococcal vaccination in adults".)
- An annual influenza vaccine should be given to all patients, particularly those with COPD [70-72]. In a randomized, placebo-controlled trial of 125 patients with COPD, vaccination reduced the incidence of influenza by 76 percent, regardless of the severity of underlying COPD [70]. The influenza vaccination itself does not increase the risk of acute exacerbation [73]. (See "Seasonal influenza vaccination in adults".)

Rehabilitation — Comprehensive pulmonary rehabilitation has been shown to improve exercise capacity, improve quality of life, decrease dyspnea, and decrease health care utilization [74-78]. In addition, it may reduce mortality [78]. Given these benefits, which have been shown to persist for up to 18 months, pulmonary rehabilitation should be considered as an addition to medication therapy for symptomatic patients who have GOLD Stage II, III, or IV COPD (table 2) [65]. (See "Pulmonary rehabilitation in COPD".)

Patient education — Patient education is an important part of managing patients with COPD and is a routine component of pulmonary rehabilitation. (See 'Information for patients' below.) Topics about which patients should be informed include reducing risk factors, appropriate administration and use of medications, recognizing and treating exacerbations, minimizing dyspnea, recognizing and treating complications, using long-term supplemental oxygen, and making end-of-life decisions (table 3). Discussions about advance directives and end-of-life care are an important component of management of

COPD, particularly for patients who have advanced disease (eg, GOLD stage III or IV) [79].

Patient education encourages self-management by the patient, as well as partnership between the patient and clinician. The effects include enhanced health, better adherence to the treatment plan, fewer hospitalizations, and fewer emergency visits [80-82].

Nutrition — More than 30 percent of patients with severe COPD have protein-calorie malnutrition. This is associated with increased mortality, impaired respiratory muscle function, and diminished immune competence. High caloric dietary supplements and megestrol acetate (Megace, an appetite stimulant) have been used in an effort to combat malnutrition. However, there is no evidence that either imparts long-term benefit [83]. (See "Nutritional support in advanced lung disease".)

Oxidative damage due to oxidant-antioxidant imbalance has been proposed as a cause of COPD. Thus, it has been hypothesized that antioxidants may prevent disease progression. However, controlled clinical trials are needed before antioxidant vitamins can be recommended for the routine management of patients with stable COPD.

Other — Opiates may be of benefit in selected patients, such as those with severe dyspnea. However, careful monitoring and follow-up is required because opiates can depress the respiratory drive. Noninvasive ventilatory support may also be useful in the treatment of acute or severe chronic respiratory failure. (See "Nocturnal ventilatory support in COPD".)

Psychoactive agents and cognitive behavioral therapy can be helpful to selected patients, such as those with anxiety or depression [84-86]. Respiratory stimulants are not beneficial to hypercapnic patients with COPD.

SURGERY — Carefully selected patients may benefit from lung volume reduction surgery (LVRS) or lung transplantation [87].

Lung volume reduction surgery — The National Emphysema Treatment Trial (NETT) enrolled 1218 patients with severe emphysema and compared lung volume reduction surgery (LVRS) to maximal medical therapy [88]. Following a baseline assessment, the patients underwent six to ten weeks of mandatory pulmonary rehabilitation and were then randomly assigned to LVRS or continued medical therapy. The efficacy of LVRS varied among patient groups, but there was an overall survival advantage that was most marked in patients with upper lobe emphysema and low exercise capacity. On the other hand, safety monitoring detected a marked increase in early mortality in patients with an FEV1 <20 percent predicted and either a DLCO <20 percent predicted or homogeneous changes on chest CT; enrollment of such patients was discontinued [89]. (See "Lung volume reduction surgery in COPD".)

Transplantation — The decision to proceed with lung transplantation for severe COPD is complex. Ample evidence suggests that functional capacity is improved following the procedure, but the presence of a survival benefit is less clear (figure 1) [90-92]. (See "Lung

transplantation: An overview" and "Lung transplantation: General guidelines for recipient selection", section on 'Chronic obstructive pulmonary disease (COPD)',).

It is important to define disease severity as precisely as possible in order to determine which patients have the most urgent need for lung transplantation and are likely to have the longest survival after transplantation [93]. Guidelines for timing a referral for a transplant evaluation for patients with COPD and emphysema due to alpha-1 antitrypsin deficiency include [90]:

- BODE index >5
- Post-bronchodilator FEV1 <25 percent of predicted
- Resting hypoxemia, defined as PaO2 <55 to 60 mmHg
- Hypercapnia
- Secondary pulmonary hypertension
- Accelerated decline in FEV1

Transplantation is usually deferred until the BODE index is seven or higher, the FEV1 is below 20 percent of predicted, the diffusing capacity for carbon monoxide (DLCO) is below 20 percent of predicted, there is a homogeneous distribution of emphysema, or the clinical course becomes more aggressive with life-threatening exacerbations (calculator 1) [88,90]. (See "Natural history and prognosis of COPD", section on 'BODE index' and "Overview of pulmonary hypertension", section on 'Definition'.)

FUTURE DIRECTIONS — Several novel therapies for COPD are being investigated. These therapies target inflammatory signaling pathways [94].

PDE-4 inhibitors — Phosphodiesterase-4 (PDE-4) inhibition decreases inflammation and promotes airway smooth muscle relaxation [95-100]. Cilomilast and roflumilast are highly specific, oral, second-generation PDE-4 inhibitors being considered for use in patients with asthma and COPD [101-104]. Their effects are illustrated by the following trials [105-108]:

- In a double-blind trial, 647 patients with COPD were randomly assigned to receive cilomilast (15 mg) or placebo twice per day for 24 weeks [105]. Patients who received cilomilast had an improved FEV1 (+10 versus -30 mL) and an improved dyspnea score. In addition, more patients were exacerbation-free in the cilomilast group (74 versus 62 percent).
- Roflumilast significantly improved prebronchodilator FEV1 and decreased the rate of moderate to severe exacerbations in a 52 week, randomized trial of 3091 patients with COPD [108]. Compared to placebo, roflumilast decreased exacerbations (17 percent [95%, CI 8-25]).
- In 24 week trials, 933 patients with moderate to severe COPD were randomly assigned to roflumilast plus salmeterol or salmeterol alone and 743 patients were randomly assigned to roflumilast plus tiotropium or tiotropium alone [109]. Roflumilast significantly improved the primary endpoint, the prebronchodilator FEV1, in both trials. However, side effects of nausea, diarrhea, and weight loss were more frequent in the roflumilast groups.

For both roflumilast and cilomilast, the magnitude of the benefits on lung function is modest compared to currently available bronchodilators. Whether PDE-4 inhibitors will also benefit other outcomes (eg, exercise tolerance, exacerbation frequency, quality of life) when other recommended COPD therapies are used concurrently (eg, long-acting bronchodilators, inhaled glucocorticoids) is unknown. Additional studies are necessary before either PDE-4 inhibitor can be recommended for routine use in patients with stable COPD.

Antiproteases — Recognition of alpha-1 antitrypsin deficiency as a cause of emphysema increased awareness that an imbalance of various proteases and antiproteases can cause COPD. For patients with alpha-1 antitrypsin deficiency, research suggests that infusions of pooled human plasma alpha-1 antitrypsin (so-called augmentation therapy) may slow the rate of disease progression. The use of antiproteases to treat alpha-1 deficiency is discussed separately. (See "Treatment of alpha-1 antitrypsin deficiency".)

New antiproteinases are at various stages of development, including compounds designed to block the effects of neutrophil elastase and matrix metalloproteinases [94]. However, these agents have not undergone large-scale clinical trials and remain unproven.

INFORMATION FOR PATIENTS — Educational materials on this topic are available for patients. (See "Patient information: Chronic obstructive pulmonary disease (COPD, including emphysema)" and "Patient information: Chronic obstructive pulmonary disease (COPD) treatments".) These topic reviews may be printed or emailed for your use. Patients may be referred to the public web site, www.uptodate.com/patients, which includes these and other topics.

SUMMARY AND RECOMMENDATIONS

- Chronic obstructive pulmonary disease (COPD) is a common condition with a high mortality. (See 'Introduction' above.)
- A staging system for COPD severity has been established by The Global Initiative for Chronic Obstructive Lung Disease (GOLD) (table 1). This staging system defines disease severity according to airflow limitation. It can be used as a guide for the management of patients with stable COPD (table 2). (See 'Assessing disease severity' above.)
- For all patients with COPD, we recommend that a short-acting bronchodilator be prescribed for use on an as-needed basis for intermittent increases in dyspnea (Grade 1A). The purpose of the short-acting bronchodilator is to reduce symptoms and improve lung function. We suggest that a short-acting beta agonist plus a short-acting anticholinergic be prescribed, rather than either alone, to achieve greater benefit (Grade 2B). Monotherapy with either is acceptable. (See 'Short-acting bronchodilators' above.)
- For patients in whom intermittent short-acting bronchodilators are insufficient to control symptoms, we recommend adding a regularly scheduled long-acting inhaled bronchodilator (Grade 1B). The purpose of the long-acting inhaled bronchodilator is to improve symptoms, improve lung function, and reduce the frequency of exacerbations. In our clinical practice, we prefer the long-acting inhaled

anticholinergic because most of the effects of the currently available once daily anticholinergic are superior to the effects of the twice daily beta agonists that are available. However, either is acceptable therapy. Theophylline is the least preferred long-acting bronchodilator option because its effects are modest and toxicity is a concern. (See 'Long-acting bronchodilators' above.)

- For patients who continue to have symptoms or repeated exacerbations despite an optimal long-acting inhaled bronchodilator regimen, we suggest adding an inhaled glucocorticoid (Grade 2B). In our clinical practice:

- - We add an inhaled glucocorticoid alone when the existing long-acting inhaled bronchodilator regimen includes a long-acting inhaled beta agonist.
- - We add the combination of an inhaled glucocorticoid plus a long-acting inhaled beta agonist when the existing long-acting inhaled bronchodilator regimen does not include a long-acting inhaled beta agonist.

An inhaled glucocorticoid may be warranted earlier (ie, at the same time that the long-acting inhaled bronchodilator is initiated) if there are signs of inflammation or an asthmatic component to the COPD. (See 'Inhaled glucocorticoids' above.)

- For symptomatic patients with GOLD Stage II, III, or IV COPD, we recommend pulmonary rehabilitation (Grade 1B). The purpose of pulmonary rehabilitation is to improve symptoms, exercise capacity, and quality of life. (See 'Rehabilitation' above.)
- We recommend long-term oxygen therapy in all patients with COPD who have chronic hypoxemia (Grade 1A). (See 'Oxygen' above.)
- All patients with COPD should be advised to quit smoking, educated about COPD, and given a yearly influenza vaccination. In addition, the pneumococcal polysaccharide vaccine should be given to patients who are ≥65 years old, or who are younger than 65 years with a forced expiratory volume in one second (FEV1) less than 40 percent. (See 'Smoking cessation' above and 'Patient education' above and 'Vaccinations' above.)
- Patients who continue to have significant symptoms despite the above interventions may be considered for surgical therapy. (See 'Surgery' above.)

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Diagnosis and treatment of infection in acute exacerbations of chronic obstructive pulmonary disease

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INTRODUCTION — The Global Initiative for Chronic Obstructive Lung Disease (GOLD) - a report produced by the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO) - defines an exacerbation of chronic obstructive pulmonary disease (COPD) as an acute increase in symptoms beyond normal day-to-day variation [1]. This generally includes one or more of the following cardinal symptoms:

- Cough increases in frequency and severity
- Sputum production increases in volume and/or changes character
- Dyspnea increases

Constitutional symptoms, a decrease in pulmonary function, and tachypnea are variably present during an exacerbation, but the chest radiograph is usually unchanged [1-3]. In the presence of severe underlying airflow obstruction, an exacerbation can cause respiratory failure and death.

The role of infection and antibiotic therapy in acute exacerbations of COPD will be reviewed here. Precipitants, risk factors, and other interventions (eg, bronchodilators, glucocorticoids, oxygen, and mechanical ventilation) are discussed separately. (See "Management of acute exacerbations of chronic obstructive pulmonary disease" and "Mechanical ventilation in acute respiratory failure complicating COPD".)

ETIOLOGY — It is estimated that 70 to 80 percent of exacerbations of COPD are due to respiratory infections. The remaining 20 to 30 percent are due to environmental pollution or have an unknown etiology [4]. Viral and bacterial infections cause most exacerbations, whereas atypical bacteria are a relatively uncommon cause (table 1) [5,6].

Viral infection — Viruses can be detected in one-third to two-thirds of exacerbations using culture, serology, and polymerase chain reaction (PCR)-based methods. The most common viruses associated with exacerbations of COPD are rhinoviruses [7]. Influenza, parainfluenza, coronavirus, and adenovirus are also common during exacerbations [7-14]. Respiratory syncytial virus and human metapneumovirus were more recently associated with exacerbations [15,16].

Identification of a virus in the sputum sample of a patient having a COPD exacerbation is relatively common and does not necessarily mean that this is the cause of the exacerbation. In fact, such viruses have been found in up to 15 percent of asymptomatic individuals with stable COPD using sensitive PCR-based assays [7,9,13,14]. Influenza virus is an exception since asymptomatic carriage is unusual.

The mechanisms by which viruses induce exacerbations have been partially elucidated. Viral infection of the airway epithelial cells induces inflammation [17]. This causes airway epithelial damage, muscarinic receptor stimulation, and induction of inflammatory mediators (eg, cytokines, chemokines) [18]. Airway eosinophilia is associated with viral mediated exacerbations, which highlights the importance of the host response to infection and its impact on both inflammation and symptoms [14].

Bacterial infection — Bacterial infections appear to trigger one-third to one-half of COPD exacerbations. Nontypeable Haemophilus influenzae, Moraxella catarrhalis, and Streptococcus pneumoniae are the bacteria most frequently isolated bronchoscopically from patients having an exacerbation of COPD [19-25]. Pseudomonas aeruginosa and Enterobacteriaceae are also commonly isolated, particularly from patients with severe COPD.

Exacerbations of COPD are strongly associated with acquisition of a new strain of H. influenzae, M. catarrhalis, S. pneumoniae, or P. aeruginosa [25-30]. As a result, it has been proposed that acquisition of a new bacterial strain plays a central role in the pathogenesis of an exacerbation. This hypothesis is supported by the following observations:

- Exacerbations with new bacterial strains are more likely to be associated with a humoral immune response — In one study, exacerbations with a new strain of H. influenzae were significantly more likely to be associated with a humoral immune response than exacerbations with preexisting strains of H. influenzae (61 versus 21 percent) [31]. These new antibodies were strain specific. M. catarrhalis and S. pneumoniae also induce an antibody response that is measurable following an exacerbation of COPD [32-34].
- Exacerbations with new bacterial strains are associated with a more robust inflammatory response — Exacerbations of COPD with a new strain of bacteria have been associated with more intense neutrophilic airway inflammation and systemic inflammation than exacerbations not associated with a change in preexisting bacterial strains or recovery of pathogenic bacteria [35]. Resolution of the airway inflammation is related to eradication of pathogenic bacteria from sputum and resolution of clinical symptoms. In an animal model, new strains of H. influenzae that were known to be associated with COPD exacerbation caused significantly more airway neutrophil recruitment than colonizing strains of H. influenzae [36].

Most of the human studies were performed in patients with COPD who had chronic bronchitis because expectorated sputum could be obtained easily. Thus, the degree to which the data can be generalized to exacerbations in patients with COPD who do not have

chronic bronchitis is unknown. (See "Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis, and staging", section on 'Types of COPD'.)

The idea that exacerbations of COPD are due to acquisition of a new strain of bacteria has largely replaced the older hypothesis that increases in the concentration of colonizing bacteria are the primary cause of exacerbations. The older theory was largely disproven by a comprehensive analysis of the relationship among sputum bacterial concentrations, exacerbation occurrence, and new pathogen acquisition [37]. The analysis demonstrated that an increase in bacterial load is not a cause of exacerbation.

Atypical bacteria — There are conflicting data regarding the incidence of atypical bacterial infection in patients having an exacerbation of COPD. This is related, in large part, to the varying criteria used to diagnose exacerbation and infection. The incidence of Chlamydophila pneumoniae in exacerbations of COPD appears to be 3 to 5 percent (Mycoplasma pneumoniae and Legionella spp. are even more rare) if one considers only studies using rigorous methodology that excluded pneumonia and defined infection as a strict fourfold increase in titer or a positive culture [10,38,39].

Coinfection — Coinfection is increasingly being considered in studies looking at the pathogenesis of COPD exacerbation. Such studies categorize exacerbations of COPD due to respiratory infection as being caused by viral infection alone, bacterial infection alone, or both [14,40,41]. Exacerbations were equally distributed across the three categories in one study [14].

Coinfection appears to increase the severity of COPD exacerbations. In a study of inpatients, coinfection was associated with a greater decrement of lung function and longer hospitalization [14]. In a similar study of outpatients, coinfection was associated with more symptoms, a larger fall in the forced expiratory volume in one second (FEV1), higher bacterial loads, and systemic inflammation [40].

DIAGNOSIS — It would be advantageous if patients whose COPD exacerbations are due to bacterial infection could be identified. This would allow antibiotic therapy to be targeted to those who are most likely to benefit. However, detection of such infections is not routinely possible because sputum cultures are unreliable and molecular methods are not widely available.

Sputum gram stain and culture — Sputum gram stain and cultures are often not useful for identifying bacterial infection in patients with COPD exacerbations for the following reasons:

- Gram stain and culture of expectorated sputum are similar during exacerbations and stable disease [8]. In other words, they do not distinguish between true pathogens and colonizing flora. The molecular typing studies cited in the preceding section that showed that new bacterial strains are more often associated with exacerbations are specialized tests that are not available for routine clinical use.
- The most common bacterial pathogens (H. influenzae, M. catarrhalis, S. pneumoniae) are frequently difficult to isolate in sputum, which increases the

likelihood of a false-negative result. In one study that collected sequential sputum cultures from patients with stable COPD, molecular typing revealed that apparently identical bacterial strains of H. influenzae were intermittently recovered, suggesting that false-negative culture results were common [42]. Support for this hypothesis was provided by the observation that strain-specific H. influenzae DNA was detected in some culture-negative sputum samples. H. influenzae is particularly problematic because H. haemolyticus, which is not a pathogen, is frequently misidentified as H. influenzae [27].

In recognition of these limitations, the 2007 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and the 2001 clinical practice guidelines from the American College of Physicians concluded that sputum cultures should NOT be performed during most exacerbations of COPD [1,43]. A possible exception recognized by the GOLD guidelines is that sputum cultures may be helpful in patients who are strongly suspected of having a bacterial infection, but fail to respond to initial antibiotic therapy [1]. However, even these cultures should be interpreted with caution because of their unreliability. (See "Sputum cultures for the evaluation of bacterial pneumonia".)

Risk factors for Pseudomonas — The value of sputum gram stain and culture is clearer during exacerbations in patients who have risk factors for Pseudomonas infection. These risk factors include recent hospitalization (≥2 days' duration during the past 90 days), frequent administration of antibiotics (≥4 courses within the past year), severe COPD (FEV1 <50 percent of predicted), isolation of P. aeruginosa during a previous exacerbation, colonization during a stable period, and systemic glucocorticoid use [1,44,45].

In contrast to H. influenzae, M. catarrhalis, and S. pneumoniae, Pseudomonas spp can easily be recovered from expectorated sputum obtained before initiating therapy. In addition, the susceptibility pattern of Pseudomonas is unpredictable, making the susceptibility results important for guiding the choice of antibiotic.

Sputum purulence — Sputum purulence may be a marker of bacterial infection during an exacerbation of COPD. In one bronchoscopic study of 40 patients with COPD exacerbations, more patients with purulent sputum had bronchial infection than patients with mucoid sputum (77 versus 6 percent) [46]. Sputum purulence correlates with increased airway bacterial concentrations and sputum neutrophilia [47]. Based on these observations, we believe that sputum purulence is an important, but not absolute, indicator of bacterial infection in patients with an exacerbation of COPD.

ANTIBIOTIC THERAPY — Treatment of COPD exacerbations often includes antibiotic therapy.

Rationale — The use of antibiotics in exacerbations of COPD is based on placebo-controlled trials and retrospective population studies that found that antibiotics improve clinical outcomes in many patients having an exacerbation of COPD [48-53].

One of the largest and most rigorous trials was a double-blind, randomized, placebo-controlled trial of 173 patients with 362 exacerbations over a three and one-half year period

[48]. Antibiotic therapy increased the likelihood of clinical improvement, defined as resolution of symptoms without additional intervention (68 versus 55 percent with placebo). Improvement was most frequent in patients with a severe exacerbation (63 versus 43 percent with placebo) and was not seen with a mild exacerbation. Similar findings were noted in a systematic review of randomized, placebo-controlled trials [49]; however, several of the trials were performed more than 20 years ago with antibiotics that were different than those that are currently used.

In a later randomized trial of 93 patients with severe exacerbations requiring mechanical ventilation, antibiotic therapy (ofloxacin) significantly decreased mortality (4 versus 22 percent with placebo) and significantly reduced the need for additional courses of antibiotics, the duration of mechanical ventilation, and the duration of hospital stay [50]. In a more recent meta-analysis of 11 placebo-controlled trials, the beneficial effect of antibiotics was clearly demonstrated in moderate to severe exacerbations in terms of mortality, clinical failure, and resolution of sputum purulence [51]. Diarrhea was the most common adverse effect.

In the multivariate analysis of a retrospective cohort study that included 84,621 patients who were hospitalized patients with acute exacerbations of COPD, the risk of treatment failure was lower in those who received antibiotics during the first two hospital days compared with those who were treated later or not at all (odds ratio 0.87, 95% CI 0.82-0.92); treatment failure was a composite endpoint defined as the initiation of mechanical ventilation after the second hospital day, inpatient mortality, or readmission for acute exacerbations of COPD within 30 days of discharge [53].

A population-based cohort study evaluated the risk of subsequent COPD exacerbations among nearly 19,000 patients treated for an exacerbation with oral glucocorticoids with or without antibiotics [52]. Median time to the second exacerbation was significantly longer among patients who received antibiotics plus oral glucocorticoids compared with those who received oral glucocorticoids alone (418 versus 321 days); median time between the second and third exacerbations was also longer (240 versus 127 days). Mortality during follow-up was also lower in patients who received antibiotics (hazard ratio 0.82, 99% CI 0.66-0.98).

On the basis of these studies, most clinical practice guidelines recommend antibiotic treatment of moderate to severe exacerbations. There is insufficient evidence to support antibiotic treatment of mild exacerbations. In addition, none of the trials to date have shown additive benefit with antibiotics over that provided by corticosteroids in the treatment of exacerbations. Trials to address these issues are ongoing or being planned.

Indications — To try to maximize the benefit of antibiotic therapy, many clinical practice guidelines recommend antibiotic therapy only for those patients who are most likely to have bacterial infection or are most ill. The GOLD guidelines recommend antibiotic therapy for patients who have the following features: a severe exacerbation requiring mechanical ventilation (noninvasive or invasive) or an exacerbation with increased sputum purulence plus either increased dyspnea or increased sputum volume [1].

We vary slightly from the GOLD guidelines in our clinical practices:

- We recommend antibiotics in patients with a moderate to severe COPD exacerbation, which is defined as having at least two of the three cardinal symptoms — increased dyspnea, increased sputum volume, or increased sputum purulence — or requiring hospitalization.
- We do NOT initiate antibiotic therapy in patients whose exacerbation is mild, which we define as having only one of the three cardinal symptoms and not requiring hospitalization or ventilatory assistance (either invasive or noninvasive).

Choice of antibiotic — The optimal antibiotic regimen for the treatment of exacerbations of COPD has not been determined. We use a "risk stratification" approach when selecting initial antibiotic therapy. Specifically, we prescribe a broader antibiotic regimen for patients who have risk factors for a poor outcome. Risk factors include older age (>65 years), comorbid conditions (especially cardiac disease), severe underlying COPD (defined as FEV1 <50 percent), frequent exacerbations (three or more per year), and antimicrobial therapy within the past three months [54-56]. This approach is illustrated in separate algorithms for selection of antibiotics in outpatients (figure 1) and inpatients (figure 2).

The risk stratification scheme recognizes that some treatment failures are probably related to ineffective antibiotic treatment and that some patients cannot afford to experience treatment failure. The same approach has been advocated for other community-acquired infections (eg, pneumonia, acute sinusitis) because it addresses concerns about disease heterogeneity, antibiotic resistance, and judicious antibiotic use [5,6,54]. However, this approach has not been shown in prospective controlled trials to improve clinical outcomes.

The initial antibiotic regimen should target likely bacterial pathogens (H. influenzae, M. catarrhalis, and S. pneumoniae in most patients) and take into account local patterns of antibiotic resistance [57]. P. aeruginosa and Enterobacteriaceae can occur in patients with severe COPD [54]. Risk factors for P. aeruginosa infection are described above. (See 'Risk factors for Pseudomonas' above.)

Historically favored (ie, first-line) antibiotics based upon randomized trials include doxycycline, trimethoprim-sulfamethoxazole, and amoxicillin [43]. However, amoxicillin is no longer considered a first-line agent because it is inactive against most nontypeable H. influenzae and M. catarrhalis.

Other (ie, second-line) antibiotics are also logical choices for outpatients based upon in vitro activity and trials showing efficacy that is comparable, but usually not superior, to doxycycline and trimethoprim-sulfamethoxazole. Antibiotics in this category include amoxicillin-clavulanate, azithromycin, cefpodoxime, cefprozil, cefuroxime, loracarbef, and the fluoroquinolones. In patients with complicated COPD and risk factors for Pseudomonas who do not have indications for hospitalization, we suggest ciprofloxacin (figure 1). (See 'Risk factors for Pseudomonas' above.)

The majority of patients with COPD exacerbations are treated as outpatients. There is a separate treatment algorithm for patients requiring hospitalization (figure 2). The antibiotic choice for such patients depends upon the risk of Pseudomonas. For hospitalized patients with risk factors for Pseudomonas, antibiotic choices include levofloxacin, cefepime,

ceftazidime, and piperacillin-tazobactam. Hospitalized patients without risk factors for Pseudomonas can be treated with a respiratory fluoroquinolone (levofloxacin, moxifloxacin) or a third-generation cephalosporin (ceftriaxone or cefotaxime).

Comparisons — The efficacy of first-line and second-line antibiotics were compared in a meta-analysis of 12 randomized trials involving more than 2100 patients with exacerbations of COPD [58]. Second-line antibiotics were significantly more likely than first-line antibiotics to achieve treatment success, defined as resolution or improvement of symptoms (OR 0.51, 95% CI 0.34-0.75). There was no difference in mortality or adverse effects.

Several studies have compared the efficacy of different second-line antibiotics to each other. A meta-analysis of 19 randomized trials (7405 patients with exacerbations of COPD) compared the effectiveness of macrolides, fluoroquinolones, and amoxicillin-clavulanate [59]. The macrolides included azithromycin and clarithromycin, while the fluoroquinolones included levofloxacin, moxifloxacin, and gemifloxacin. Antibiotic selection did not affect short-term treatment success, defined as resolution or improvement of symptoms. However, fluoroquinolones were associated with a higher rate of microbiologic success and, in the 26 weeks following therapy, a lower rate of recurrence. Amoxicillin-clavulanate was associated with more adverse effects (mostly diarrhea) than the other drug classes.

Duration — The duration of antibiotic therapy for patients with a COPD exacerbation is usually three to seven days, depending upon the response to therapy. A meta-analysis that compared five days to seven or more days of antimicrobial therapy (fluoroquinolones, cefixime, or clarithromycin) for exacerbations of COPD found no difference in outcome between the two groups, although there were fewer adverse events among patients who received a five-day course [60].

Patients who are initially started on parenteral antibiotics should be switched to an oral regimen when able to take medications orally.

Antiviral therapy — Patients whose COPD exacerbation was triggered by influenza virus should be treated with antiviral therapy according to current recommendations and based on the predicted susceptibility patterns of the

circulating strains. Inhaled zanamivir is contraindicated in this patient population due to the risk of airway reactivity. Several other agents agents can be used such as oral oseltamivir, or in certain situations, intravenous zanamivir or peramivir. (See "Treatment of seasonal influenza in adults".)

PREVENTION — Patients with COPD should receive influenza vaccine annually and pneumococcal polysaccharide vaccine once, with a single booster five years later if the patient is now 65 years or older and was less than 65 years old when the initial vaccination was given [61,62]:

- The utility of influenza vaccine is well established for reducing both the rate and severity of symptoms due to influenza, including respiratory symptoms. A meta-

analysis of 11 trials, including six specifically performed in patients with COPD, found a significant reduction in the number of exacerbations per patient compared with placebo [63]. (See "Seasonal influenza vaccination in adults".)

- For pneumococcal vaccine, a meta-analysis of four trials that assessed the effect on patients with COPD found no evidence of a significant impact on morbidity or mortality [64]. One trial provided data on acute exacerbations of COPD, with no significant effect of vaccination, and a second trial found no significant effect on hospitalizations for acute exacerbations. The recommendation for the pneumococcal vaccine in patients with COPD is based upon studies suggesting a reduced frequency of pneumococcal pneumonia and pneumococcal bacteremia. (See "Pneumococcal vaccination in adults".)

Some clinicians advocate prophylactic antibiotics for patients with severe exacerbations, especially those that occur seasonally. This approach is largely based upon trials conducted before 1970, some of which showed a benefit [65-67]. A meta-analysis of nine such trials found a significant reduction in the number of days of disability (mean of one day per month) and a nonsignificant reduction in the number of acute exacerbations (0.12 exacerbations per patient per year) [68]. These possible benefits must be weighed against a small increase in side effects and concerns about antibiotic resistance [68].

Taken together, these results do not support widespread use of prophylactic antibiotics in COPD. Two large trials are currently being conducted to assess the impact of prophylactic antibiotics in COPD. One of the trials is testing intermittent courses of a fluoroquinolone, while the other is evaluating a macrolide given daily. These trials will provide new information about the role of prophylactic antibiotics in COPD.

Interventions to prevent exacerbations of COPD that are unrelated to infection are discussed separately. (See "Management of acute exacerbations of chronic obstructive pulmonary disease", section on 'Prevention'.)

SUMMARY AND RECOMMENDATIONS

- An exacerbation of COPD is an acute increase in symptoms beyond normal day-to-day variation. Specifically, cough increases in frequency and severity, sputum production increases in volume or changes character, and dyspnea increases. (See 'Introduction' above.)
- Most exacerbations of COPD are due to respiratory infection or environmental pollution. Respiratory infections that can cause exacerbations include viral, bacterial, and mixed infections. (See 'Etiology' above.)
- Sputum cultures should not be performed during most exacerbations of COPD. (See 'Diagnosis' above.)
- Antibiotic therapy increases the likelihood of clinical improvement in patients having an exacerbation of COPD, particularly in patients with a moderate to severe exacerbation. Among patients requiring mechanical ventilation, antibiotic therapy may provide a mortality benefit. (See 'Rationale' above.)
- For patients whose exacerbation of COPD is mild (defined as not requiring hospitalization or mechanical ventilation and having only one of the three cardinal

symptoms of increased dyspnea, sputum purulence, or sputum production), we suggest that antibiotics NOT be prescribed (Grade 2B). (See 'Indications' above.)

- For patients whose exacerbation of COPD is moderate to severe (defined as requiring hospitalization or having at least two of the three cardinal symptoms), we recommend antibiotic therapy (Grade 1B). (See 'Indications' above and 'Choice of antibiotic' above.)
- The optimal antibiotic regimen for the treatment of exacerbations of COPD has not been determined. We use a "risk stratification" approach when selecting initial antibiotic therapy. The initial antibiotic regimen should target likely bacterial pathogens and take into account local patterns of antibiotic resistance. (See 'Choice of antibiotic' above.)
- The usual duration of antibiotic therapy is three to seven days, depending upon the response to therapy. (See 'Duration' above.)
- For most patients with COPD, we suggest that antibiotics NOT be administered for the purpose of preventing exacerbations (Grade 2C). (See 'Prevention' above.)

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