Global Initiative for Chronic **O**bstructive **L** ung **D**isease

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

UPDATED 2014

GLOBAL INITIATIVE FOR
CHRONIC OBSTRUCTIVE LUNG DISEASE

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (UPDATED 2014)

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF COPD (UPDATED 2014)

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GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF COPD (REVISED 2011)

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PREFACE

In 2011, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) released a consensus report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD*. It recommended a major revision in the management strategy for COPD that was presented in the original 2001 document. Updated reports released in January 2013 and January 2014 are based on scientific literature published since the completion of the 2011 document but maintain the same treatment paradigm. Assessment of COPD is based on the patient's level of symptoms, future risk of exacerbations, the severity of the spirometric abnormality, and the identification of comorbidities.

The GOLD report is presented as a "strategy document" for health care professionals to use as a tool to implement effective management programs based on available health care systems. The quadrant management strategy tool is designed to be used in any clinical setting; it draws together a measure of the impact of the patient's symptoms and an assessment of the patient's risk of having a serious adverse health event in the future. More and more evidence is being produced to evaluate this strategy*. Evidence will continue to be evaluated by the GOLD committees and management strategy recommendations modified as required.

GOLD has been fortunate to have a network of international distinguished health professionals from multiple disciplines. Many of these experts have initiated investigations of the causes and prevalence of COPD in their countries, and have developed innovative approaches for the dissemination and implementation of the GOLD management strategy. The GOLD initiative will continue to work with National Leaders and other interested health care professionals to bring COPD to the attention of governments, public health officials, health care workers, and the general public to raise awareness of the burden of COPD and to develop programs for early detection, prevention and approaches to management.

We are most appreciative of the unrestricted educational grants from Almirall, AstraZeneca, Boehringer-Ingelheim, Chiesi, Forest Laboratories, GlaxoSmithKline, Merck Sharp & Dohme, Mylan, Nonin Medical, Novartis, Pearl Therapeutics, Pfizer, Quintiles, and Takeda that enabled development of this report.

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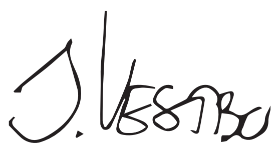

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*Lange P, Marott JL, Vestbo J, Olsen KR, Ingebrigtsen TS, Dahl M, Nordestgaard BG. Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: a study of the general population. *Am J Respir Crit Care Med.* 2012 Nov 15;186(10):975-81.

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METHODOLOGY AND SUMMARY OF NEW RECOMMENDATIONS GLOBAL STRATEGY FOR DIAGNOSIS, MANAGEMENT AND PREVENTION OF COPD 2014 UPDATE[1]

When the Global Initiative for Chronic Obstructive Lung Disease (GOLD) program was initiated in 1998, a goal was to produce recommendations for management of COPD based on the best scientific information available. The first report, *Global Strategy for Diagnosis, Management and Prevention of COPD* was issued in 2001. In 2006 and again in 2011 a complete revision was prepared based on published research. These reports, and their companion documents, have been widely distributed and translated into many languages and can be found on the GOLD website (www.goldcopd.org).

The GOLD Science Committee[2] was established in 2002 to review published research on COPD management and prevention, to evaluate the impact of this research on recommendations in the GOLD documents related to management and prevention, and to post yearly updates on the GOLD website. Its members are recognized leaders in COPD research and clinical practice with the scientific credentials to contribute to the task of the Committee and are invited to serve in a voluntary capacity.

The first update of the 2011 revised report was released in January 2013. This second update, released January 2014, is based on the impact of publications from January 1 through December 31, 2013. Posted on the website along with the updated documents is a list of all the publications reviewed by the Committee.

Process: To produce the updated documents a Pub Med search is completed using search fields established by the Committee: 1) *COPD, All Fields, All Adult: 19+ years, only items with abstracts, Clinical Trial, Systematic Reviews, Human*. The first search included publications for January 1 – March 31 for review by the Committee during the ATS meeting. The second search included publications for April 1 – August 31 for review by the Committee during the ERS meeting. The third search for publications from September – December were reviewed in December by the GOLD Board of Directors. Publications in peer review journals not captured by Pub Med can be submitted to the Chair, GOLD Science Committee, providing an abstract and the full paper are submitted in (or translated into) English.

Members of the Committee receive a summary of citations and all abstracts. Each abstract is assigned to two Committee members, although all members are offered the opportunity to provide an opinion on any abstract. Members evaluate the abstract or, up to her/his judgment, the full publication, by answering four specific written questions from a short questionnaire, and to indicate if the scientific data presented impacts on recommendations in the GOLD report. If so, the member is asked to specifically identify modifications that should be made.

The GOLD Science Committee meets twice yearly to discuss each publication that was considered by at least 1 member of the Committee to potentially have an impact on the COPD management. The full Committee then reaches a consensus on whether to include it in the report, either as a reference supporting current recommendations, or to change the report. In the absence of consensus, disagreements are decided by an open vote of the full Committee. The final review and approval of all recommendations is provided by the GOLD Board of Directors at its annual meeting in December.

Recommendations by the GOLD Committees for use of any medication are based on the best evidence available from the published literature and not on labeling directives from government regulators. The Committee does not make recommendations for therapies that have not been approved by at least one regulatory agency.

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[1] The Global Strategy for Diagnosis, Management and Prevention of COPD (updated 2014), the Pocket Guide (updated 2014) and the complete list of references examined by the Committee are available on the GOLD website www.goldcopd.org.

[2] Members (2012-2013): J. Vestbo, *Chair*; A. Agusti, A. Anzueto, L. Fabbri, P. Jones, F. Martinez, N. Roche, R. Rodriguez-Roisin, D. Sin, R. Stockley, C. Volgelmeier, W. Wedzicha.

As an example of the workload of the Committee, for the 2014 update, between January and December, 2013, 292 articles met the search criteria. Of the 292 papers, 30 were identified to have an impact on the GOLD report posted on the website in January 2014 either by: A) modifying, that is, changing the text or introducing a concept requiring a new recommendation to the report; B) confirming, that is, adding or replacing an existing reference; or C) requiring modification for clarification of the text.

SUMMARY OF RECOMMENDATIONS IN THE 2014 UPDATE

A. Additions to the text

Page 17, left column, last paragraph line 5, insert statement and reference: Exercise capacity may fall in the year before death[557.]

Reference 557: Polkey MI, Spruit MA, Edwards LD, Watkins ML, Pinto-Plata V, Vestbo J, et al; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Study Investigators. Six-minute-walk test in chronic obstructive pulmonary disease: minimal clinically important difference for death or hospitalization. *Am J Respir Crit Care Med* 2013 Feb 15;187(4):382-6.

Page 23, right column, second paragraph, replace sentence on line 13 beginning with "Tiotropium has…" with: Among long-acting anticholinergics, acclidinium has a duration of at least 12 hours[552] whereas tiotropium and glycopyrronium have a duration of action of more than 24 hours[209-211].

Reference 552: Jones PW, Singh D, Bateman ED, Agusti A, Lamarca R, de Miquel G,Segarra R, Caracta C, Garcia Gil E. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. *Eur Respir J* 2012 Oct;40(4):830-6.

Page 23, right column, second paragraph, insert statement and reference at the end: The long-acting anticholinergics aclidinium and glycopyrronium seem to have similar action on lung function and breathlessness as tiotropium, whereas far less data are available for other outcomes[552, 558].

Reference 552: Jones PW, Singh D, Bateman ED, Agusti A, Lamarca R, de Miquel G, Segarra R, Caracta C, Garcia Gil E. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. *Eur Respir J* 2012 Oct;40(4):830-6.

Reference 558: Kerwin E, Hébert J, Gallagher N, Martin C, Overend T, Alagappan VK, Lu Y, Banerji D. Efficacy and safety of NVA237 versus placebo and tiotropium in
patients with COPD: the GLOW2 study. *Eur Respir J* 2012 Nov;40(5):1106-14.

Page 24, left column, first paragraph, replace section beginning with "Tiotropium delivered…" to end of paragraph with: Tiotropium delivered via the Respimat® soft mist inhaler was associated with a significantly increased risk of mortality compared with placebo in a meta-analysis[519]; however, the findings of the TIOSPIR® trial showed that there was no difference in mortality or rates of exacerbation when comparing tiotropium in a dry-powder inhaler to the Respimat® inhaler[559]. Use of solutions with a facemask has been reported to precipitate acute glaucoma, probably by a direct effect of the solution on the eye.

Reference 559: Wise RA, Anzueto A, Cotton D, Dahl R, Devins T, Disse B, *et al* for the TIOSPIR Investigators. Tiotripium Respimat Inhaler and the Risk of Death in COPD. *N Engl J Med* 2013 Oct 17;369(16):1491-1501.

Page 24, right column, end of second paragraph, insert statement and references: Combinations of a long-acting beta$_2$-agonist and a long-acting anticholinergic have shown a significant increase in lung function whereas the impact on patient reported outcomes is still limited[560]. There is still too little evidence to determine if a combination of long-acting bronchodilators is more effective than a long-acting anticholinergic alone for preventing exacerbations[561].

Reference 560: Bateman ED, Ferguson GT, Barnes N, Gallagher N, Green Y, Henley M, Banerji D. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. *Eur Respir J* 2013 Dec;42(6):1484-94.

Reference 561: Wedzicha JA, Decramer M, Ficker JH, Niewoehner DE, SandstroÅNm T, Taylor AF, *et al*. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med* 2013;1:199–209

Page 26, right column, end of last paragraph, insert statement and reference: However the increased exercise capacity may not necessarily translate into increased daily physical activity[563].

Reference 563: Egan C, Deering BM, Blake C, Fullen BM, McCormack NM, Spruit MA, Costello RW. Short term and long term effects of pulmonary rehabilitation on physical activity in COPD. *Respir Med* 2012 Dec;106(12):1671-9.

Page 28, right column, second paragraph, replace heading Nutrition counseling by Nutritional support. Replace two paragraphs with statement and reference: Low-to-moderate quality evidence suggests that nutritional support promotes significant gain in weight and fat-free mass among patients with COPD, especially if malnourished. In addition, significantly greater changes from baseline have been observed in supplemented patients for six-minute walk test, respiratory muscle strength and (only in malnourished patients) overall HRQoL as measured by SGRQ. Positive effects have been observed when nutritional supplementation is proposed alone or as an adjunct to exercise training. The optimal amount and duration of supplementation are not clearly established[564].

Reference 564: Ferreira IM, Brooks D, White J, Goldstein R. Nutritional supplementation for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012 Dec 12;12:CD000998.

Page 35, left column, third paragraph line four, modify sentence to read: However, for all Group A patients, a short-acting bronchodilator used as needed is recommended as first choice based on its effect on lung function and breathlessness[565].

Reference 565: Gagnon P, Saey D, Provencher S, Milot J, Bourbeau J, Tan WC, Martel S, Maltais F. Walking exercise response to bronchodilation in mild COPD: a randomized trial. *Respir Med* 2012 Dec;106(12):1695-705.

Page 37, left column, end of first paragraph under monitoring and follow up, insert statement and reference: Comprehensive self-management or routine monitoring does not appear to show long term benefits in terms of quality of life or self efficacy over usual care alone in COPD patients in general practice[566].

Reference 566: Bischoff EW, Akkermans R, Bourbeau J, van Weel C, Vercoulen JH, Schermer TR. Comprehensive self management and routine monitoring in chronic obstructive pulmonary disease patients in general practice: randomised controlled trial. *BMJ* 2012 Nov 28;345:e7642.

Page 42, right column, first line delete "A dose of 30-40 mg prednisone per day for 10-14 days is recommended (Evidence D), and insert: A dose of 40 mg prednisone per day for 5 days is recommended (**Evidence B**)[567].

Reference 567: Leuppi JD, Schuetz P, Bingisser R, Bodmer M, Briel M, Drescher T, *et al.*. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *JAMA* 2013 Jun 5;309(21):2223-31.

Page 42, right column, insert at the end of first paragraph: Nebulised magnesium as an adjuvant to salbutamol treatment in the setting of acute exacerbations of COPD has no effect on FEV_1[568].

Reference 568: Edwards L, Shirtcliffe P, Wadsworth K, Healy B, Jefferies S, Weatherall M, Beasley R; Magnesium COPD Study Team. Use of nebulised magnesium sulphate as an adjuvant in the treatment of acute exacerbations of COPD in adults: a randomised double-blind placebo-controlled trial. *Thorax* 2013 Apr;68(4):338-43.

Page 43 at end of paragraph on Adjunct Therapies, insert statement and references; Given that patients hospitalized because of exacerbations of COPD are at increased risk of deep vein thrombosis and pulmonary embolism[570,571], thromboprophylactic measures should be enhanced[572-574].

Reference 570: Rizkallah J, Man SF, Sin DD. Prevalence of pulmonary embolism in exacerbations of COPD: a systematic review and metaanalysis. *Chest* 2009 Mar;135(3):786-93.

Reference 571: Gunen H, Gulbas G, In E, Yetkin O, Hacievliyagil SS. Venous thromboemboli and exacerbations of COPD. *Eur Respir J* 2010;35(6):1243-8.

Reference 572: Qaseem A, Chou R, Humphrey LL, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Venous thromboembolism prophylaxis in hospitalized patients:

a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2011 Nov 1;155(9):625-32.

Reference 573: Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, *et al*; American College of Chest Physicians. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012 Feb;141(2 Suppl):e195S-226S.

Reference 574: Bertoletti L, Quenet S, Laporte S, Sahuquillo JC, Conget F, Pedrajas JM, Martin M, Casado I, Riera-Mestre A, Monreal M; RIETE Investigators. Pulmonary embolism and 3-month outcomes in 4036 patients with venous thromboembolism and chronic obstructive pulmonary disease: data from the RIETE registry. *Respir Res* 2013 Jul 18;14:75.

Page 45, left column, last sentence under Home Management of Exacerbations, insert statement and three references: Accumulating data from a variety of studies indicate that telehealth in any of its current forms has not shown benefits for patients with COPD; thus, telehealth is not recommended for use with COPD patients[575-577].

Reference 575: Cartwright M, Hirani SP, Rixon L, Beynon M, Doll H, Bower P, *et al*; Whole Systems Demonstrator Evaluation Team. Effect of telehealth on quality of life and psychological outcomes over 12 months (Whole Systems Demonstrator telehealth questionnaire study): nested study of patient reported outcomes in a pragmatic, cluster randomised controlled trial. *BMJ* 2013 Feb 26;346:f653.

Reference 576: Henderson C, Knapp M, Fernández JL, Beecham J, Hirani SP, Cartwright M, *et al*; Whole System Demonstrator evaluation team. Cost effectiveness of telehealth for patients with long term conditions (Whole Systems Demonstrator telehealth questionnaire study): nested economic evaluation in a pragmatic, cluster randomised controlled trial. *BMJ* 2013 Mar 20;346:f1035.

Reference 577: Pinnock H, Hanley J, McCloughan L, Todd A, Krishan A, Lewis S, et al. Effectiveness of telemonitoring integrated into existing clinical services on hospital admission for exacerbation of chronic obstructive pulmonary disease: researcher blind, multicentre, randomised controlled trial. *BMJ* 2013 Oct 17;347:f6070.

Page 50, insert at end of chapter on COPD and Comorbidities:

Bronchiectasis: Persistent airflow obstruction is a recognized feature of some patients with a primary diagnosis of bronchiectasis. However with increasing use of computed tomography in the assessment of patients with COPD, the presence of previously unrecognized radiographic bronchiectasis is being identified[581]. This ranges from mild tubular bronchiectasis to more severe varicose change, although cystic bronchiectasis is uncommon. Whether this radiological change has the same impact as patients with a primary diagnosis of bronchiectasis remains unknown at present, although it is associated with longer exacerbations[582] and increased mortality[583].

<u>Treatment of bronchiectasis in patients with COPD:</u> Treatment should be along conventional lines for bronchiectasis with the addition of usual COPD strategies where indicated. Whether prevention of exacerbations requires more long-term use of oral or inhaled antibiotics rather than bronchodilator or inhaled corticosteroid therapy remains unknown.

<u>Treatment of COPD in patients with bronchiectasis:</u> COPD should be treated as usual, although some patients may need more aggressive and prolonged antibiotic therapy.

Reference 581: O'Brien C, Guest PJ, Hill SL, Stockley RA. Physiological and radiological characterisation of patients diagnosed with chronic obstructive pulmonary disease in primary care. *Thorax* 2000;558:635-642

Reference 582: Patel IS, Vlahos I, Wilkinson TMA, et al. Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;1704:400-407

Reference 583: Martínez-García MA, de la Rosa Carrillo D, Soler-Cataluña JJ, Donat-Sanz Y, Serra PC, Lerma MA, Ballestín J, Sánchez IV, Selma Ferrer MJ, Dalfo AR, Valdecillos MB. <u>Prognostic value of bronchiectasis in patients with moderate-to-severe chronic obstructive pulmonary disease.</u> *Am J Respir Crit Care Med* 2013 Apr 15;187(8):823-31

B. References that provided confirmation or update of previous recommendations

Page 26, left column, line 11, after reference 297, insert:
Reference 562: Tse HN, Raiteri L, Wong KY, Yee KS, Ng LY, Wai KY, Loo CK, Chan MH. High-dose N-acetylcysteine in stable COPD: the 1-year, double-blind, randomized, placebo-controlled HIACE study. *Chest* 2013 Jul;144(1):106-18.

Page 42, right column, end of first sentence under paragraph on Antibiotics, insert:
Reference 569: Vollenweider DJ, Jarrett H, Steurer-Stey CA, Garcia-Aymerich J, Puhan MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012 Dec 12;12:CD010257.

Page 42, right column, line 5 from end, insert after reference 273:
Reference 351: Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;106:196-204.

Page 48 after reference 476 in first sentence insert:
Reference 578: Almagro P, Cabrera FJ, Diez J, Boixeda R, Alonso Ortiz MB, Murio C, Soriano JB; Working Group on COPD, Spanish Society of Internal Medicine. Comorbidities and short-term prognosis in patients hospitalized for acute exacerbation of COPD: the EPOC en Servicios de medicina interna (ESMI) study. *Chest* 2012 Nov;142(5):1126-33.

Pages 48 right column, paragraph 4 after reference 546 and Page 49 left column after reference 481 insert:
Reference 579: Mainguy V, Girard D, Maltais F, Saey D, Milot J, Sénéchal M, Poirier P, Provencher S. Effect of bisoprolol on respiratory function and exercise capacity in chronic obstructive pulmonary disease. *Am J Cardiol* 2012 Jul 15;110(2):258-63
Reference 580: Stefan MS, Rothberg MB, Priya A, Pekow PS, Au DH, Lindenauer PK. Association between β-blocker therapy and outcomes in patients hospitalised with acute exacerbations of chronic obstructive lung disease with underlying ischaemic heart disease, heart failure or hypertension. *Thorax* 2012 Nov;67(11):977-84.

C. Modifications to text to correct wording

Page 35, right column, paragraph 2, second and third sentence should read: The first choice of therapy is inhaled corticosteroid plus long-acting beta2-agonist or long-acting anticholinergic, although there are conflicting findings concerning this treatment[257]; support for it mainly comes from short-term studies[257,538,539] (**Evidence B**). As second choice a combination of all three classes of drugs (inhaled corticosteroids/long-acting $beta_2$-agonist/long-acting anticholinergic) is recommended[256].

D. Inserts related to tables/figures and special topics covered by the Committee

PREFACE, page iv: A new Preface includes a statement about the quadrant management strategy.

Page 13, left column: The material on *Assessment of Symptoms* has been modified and several new references inserted.

Page 14, right column: The material on *Assessment of Exacerbation Risk* has been modified and one new reference inserted.

Page 15, right column: Figure 2.3 has been modified to reflect the new statement on page 13 related to *Assessment of Symptoms.*

Page 15, right column and page 16 left column: Text has been modified to reflect the new statements on page 13 related to *Assessment of Symptoms.*

Page 22, Table 3.3. Formulations and Typical Doses of COPD Medications, insert under heading Combination long-acting beta2-agonists plus corticosteroids in one inhaler: Vilanterol/Fluticasone furoate, 25/100 (DPI).

Page 33, left column: Table 4.2 has been modified to reflect the new statement on page 13 related to *Assessment of Symptoms.*

Page 51 Insert Chapter 7: Asthma and COPD Overlap Syndrome (ACOS)

A chapter on *Asthma and COPD Overlap Syndrome (ACOS)* is in preparation by the Science Committees of the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD). It is expected to be available with the release of the GINA 2014 document *Global Strategy for Asthma Management and Prevention* in the Spring 2014. A brief summary is included in this 2014 GOLD update; the full chapter will be posted on the GOLD website when it is available, and will appear in full in the 2015 GOLD update.

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF COPD

INTRODUCTION

Much has changed in the 10 years since the first GOLD report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD*, was published. This major revision builds on the strengths from the original recommendations and incorporates new knowledge.

One of the strengths was the treatment objectives. These have stood the test of time, but are now organized into two groups: objectives that are directed towards immediately relieving and reducing the impact of symptoms, and objectives that reduce the risk of adverse health events that may affect the patient at some point in the future. (Exacerbations are an example of such events.) This emphasizes the need for clinicians to maintain a focus on both the short-term and long-term impact of COPD on their patients.

A second strength of the original strategy was the simple, intuitive system for classifying COPD severity. This was based upon the FEV_1 and was called a staging system because it was believed, at the time, that the majority of patients followed a path of disease progression in which the severity of the disease tracked the severity of the airflow limitation. Much is now known about the characteristics of patients in the different GOLD stages – for example, their level of risk of exacerbations, hospitalization, and death. However at an individual patient level, the FEV_1 is an unreliable marker of the severity of breathlessness, exercise limitation, and health status impairment. This report retains the GOLD classification system because it is a predictor of future adverse events, but the term "Stage" is now replaced by "Grade."

At the time of the original report, improvement in both symptoms and health status was a GOLD treatment objective, but symptoms assessment did not have a direct relation to the choice of management, and health status measurement was a complex process largely confined to clinical studies. Now, there are simple and reliable questionnaires designed for use in routine daily clinical practice. These are available in many languages. These developments have enabled a new assessment system to be developed that draws together a measure of the impact of the patient's symptoms and an assessment of the patient's risk of having a serious adverse health event in the future. In turn, this new assessment system has led to the construction of a new approach to management– one that matches assessment to treatment objectives. The new management approach can be used in any clinical setting anywhere in the world and moves COPD treatment towards individualized medicine – matching the patient's therapy more closely to his or her needs.

BACKGROUND

Chronic Obstructive Pulmonary Disease (COPD), the fourth leading cause of death in the world[1], represents an important public health challenge that is both preventable and treatable. COPD is a major cause of chronic morbidity and mortality throughout the world; many people suffer from this disease for years, and die prematurely from it or its complications. Globally, the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and aging of the population[2].

In 1998, with the cooperation of the National Heart, Lung, and Blood Institute, NIH and the World Health Organization, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) was implemented. Its goals were to increase awareness of the burden of COPD and to improve prevention and management of COPD through a concerted worldwide effort of people involved in all facets of health care and health care policy. An important and related goal was to encourage greater research interest in this highly prevalent disease.

In 2001, GOLD released it first report, *Global Strategy for the Diagnosis, Management, and Prevention of COPD*. This report was not intended to be a comprehensive textbook on COPD, but rather to summarize the current state of the field. It was developed by individuals with expertise in COPD research and patient care and was based on the best-validated concepts of COPD pathogenesis at that time, along with available evidence on the most appropriate management and prevention strategies. It provided state-of-the-art information about COPD for pulmonary specialists and other interested physicians and served as a source document for the production of various communications for other audiences, including an Executive Summary[3], a Pocket Guide for Health Care Professionals, and a Patient Guide.

Immediately following the release of the first GOLD report in 2001, the GOLD Board of Directors appointed a Science Committee, charged with keeping the GOLD documents up-to-date by reviewing published research, evaluating the impact of this research on the management recommendations in the GOLD documents, and posting yearly updates of these documents on the GOLD Website. The first update to the GOLD report was posted in July 2003, based on publications from January 2001 through December 2002. A second update appeared in July 2004, and a third in July 2005, each including the impact of publications from January through December of the previous year. In January 2005, the GOLD Science Committee initiated its work to prepare a comprehensively updated version of the GOLD report; it was released in 2006. The methodology used to create the annual updated documents, and the 2006 revision, appears at the front of each volume.

During the period from 2006 to 2010, again annual updated documents were prepared and released on the GOLD Website, along with the methodology used to prepare the documents and the list of published literature reviewed to examine the impact on recommendations made in the annual updates. In 2009, the GOLD Science Committee recognized that considerable new information was available particularly related to diagnosis and approaches to management of COPD that warranted preparation of a significantly revised report. The work on this new revision was implemented in mid-2009 while at the same time the Committee prepared the 2010 update.

METHODOLOGY

In September 2009 and in May and September 2010 while preparing the annual updated reports (*http://www.goldcopd.org*), Science Committee members began to identify the literature that impacted on major recommendations, especially for COPD diagnosis and management. Committee members were assigned chapters to review for proposed modifications and soon reached consensus that the report required significant change to reach the target audiences – the general practitioner and the individuals in clinics around the world who first see patients who present with respiratory symptoms that could lead to a diagnosis of COPD. In the summer of 2010 a writing committee was established to produce an outline of proposed chapters, which was first presented in a symposium for the European Respiratory Society in Barcelona, 2010. The writing committee considered recommendations from this session throughout fall 2010 and spring 2011. During this period the GOLD Board of Directors and GOLD National Leaders were provided summaries of the major new directions recommended. During the summer of 2011 the document was circulated for review to GOLD National Leaders, and other COPD opinion leaders in a variety of countries. The names of the individuals who submitted reviews appear in the front of this report. In September 2011 the GOLD Science Committee reviewed the comments and made final recommendations. The report was launched during a symposium hosted by the Asian Pacific Society of Respirology in November 2011.

NEW ISSUES PRESENTED IN THIS REPORT

1. This document has been considerably shortened in length by limiting to Chapter 1 the background information on COPD. Readers who wish to access more comprehensive information about the pathophysiology of COPD are referred to a variety of excellent textbooks that have appeared in the last decade.

2. Chapter 2 includes information on diagnosis and assessment of COPD. The definition of COPD has not been significantly modified but has been reworded for clarity.

3. Assessment of COPD is based on the patient's level of symptoms, future risk of exacerbations, the severity of the spirometric abnormality, and the identification of comorbidities. Whereas spirometry was previously used to support a diagnosis of COPD, spirometry is now required to make a confident diagnosis of COPD.

4. The spirometric classification of airflow limitation is divided into four Grades (GOLD 1, Mild; GOLD 2, Moderate; GOLD 3, Severe; and GOLD 4, Very Severe) using the fixed ratio, postbronchodilator $FEV_1/FVC < 0.70$, to define airflow limitation. It is recognized that use of the fixed ratio (FEV_1/FVC) may lead to more frequent diagnoses of COPD in older adults with mild COPD as the normal process of aging affects lung volumes and flows, and may lead to under-diagnosis in adults younger than 45 years. The concept of staging has been abandoned as a staging system based on FEV_1 alone was inadequate and the evidence for an alternative staging system does not exist. The most severe spirometric Grade, GOLD 4, does not include reference to respiratory failure as this seemed to be an arbitrary inclusion.

5. A new chapter (Chapter 3) on therapeutic approaches has been added. This includes descriptive information on both pharmacologic and non-pharmacologic therapies, identifying adverse effects, if any.

6. Management of COPD is presented in three chapters: Management of Stable COPD (Chapter 4); Management of COPD Exacerbations (Chapter 5); and COPD and Comorbidities (Chapter 6), covering both management of comorbidities in patients with COPD and of COPD in patients with comorbidities.

7. In Chapter 4, Management of Stable COPD, recommended approaches to both pharmacologic and non-pharmacologic treatment of COPD are presented. The chapter begins with the importance of identification and reduction of risk factors. Cigarette smoke continues to be

identified as the most commonly encountered risk factor for COPD and elimination of this risk factor is an important step toward prevention and control of COPD. However, more data are emerging to recognize the importance of other risk factors for COPD that should be taken into account where possible. These include occupational dusts and chemicals, and indoor air pollution from biomass cooking and heating in poorly ventilated dwellings – the latter especially among women in developing countries.

8. In previous GOLD documents, recommendations for management of COPD were based solely on spirometric category. However, there is considerable evidence that the level of FEV_1 is a poor descriptor of disease status and for this reason the management of stable COPD based on a strategy considering both disease impact (determined mainly by symptom burden and activity limitation) and future risk of disease progression (especially of exacerbations) is recommended.

9. Chapter 5, Management of Exacerbations, presents a revised definition of a COPD exacerbation.

10. Chapter 6, Comorbidities and COPD, focuses on cardiovascular diseases, osteoporosis, anxiety and depression, lung cancer, infections, and metabolic syndrome and diabetes.

LEVELS OF EVIDENCE

Levels of evidence are assigned to management recommendations where appropriate. Evidence levels are indicated in boldface type enclosed in parentheses after the relevant statement e.g., (**Evidence A**). The methodological issues concerning the use of evidence from meta-analyses were carefully considered. This evidence level scheme (**Table A**) has been used in previous GOLD reports, and was in use throughout the preparation of this document[4].

Table A. Description of Levels of Evidence

Evidence Catagory	Sources of Evidence	Definition
A	Randomized controlled trials (RCTs). Rich body of data.	Evidence is from endpoints of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
B	Randomized controlled trials (RCTs). Limited body of data.	Evidence is from endpoints of intervention studies that include only a limited number of patients, posthoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C	Nonrandomized trials. Observational studies.	Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies
D	Panel Consensus Judgment.	This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was deemed insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above-listed criteria

CHAPTER

1

DEFINITION AND OVERVIEW

CHAPTER 1: DEFINITION AND OVERVIEW

KEY POINTS:

- *Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.*
- COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing.
- Inhaled cigarette smoke and other noxious particles such as smoke from biomass fuels cause lung inflammation, a normal response that appears to be modified in patients who develop COPD. This chronic inflammatory response may induce parenchymal tissue destruction (resulting in emphysema), and disrupt normal repair and defense mechanisms (resulting in small airway fibrosis). These pathological changes lead to air trapping and progressive airflow limitation, and in turn to breathlessness and other characteristic symptoms of COPD.

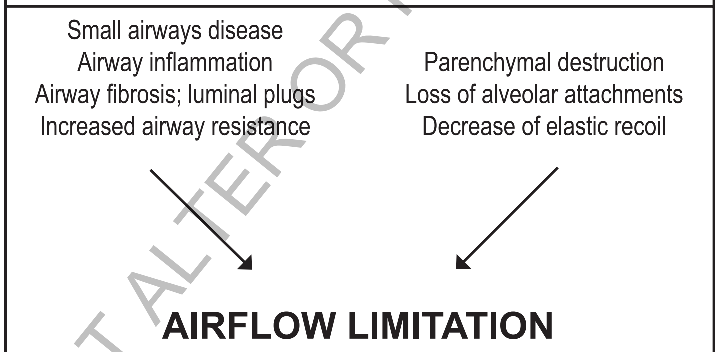
DEFINITION

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.

The chronic airflow limitation characteristic of COPD is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person (**Figure 1.1**). Chronic inflammation causes structural changes and narrowing of the small airways. Destruction of the lung parenchyma, also by inflammatory processes, leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil; in turn, these changes diminish the ability of the airways to remain open during expiration. Airflow limitation is best measured by spirometry, as this is the most widely available, reproducible test of lung function.

Many previous definitions of COPD have emphasized the terms "emphysema" and "chronic bronchitis," which are not included in the definition used in this or earlier GOLD reports. Emphysema, or destruction of the gas-exchanging surfaces of the lung (alveoli), is a pathological term that is often (but incorrectly) used clinically and describes

Figure 1.1. Mechanisms Underlying Airflow Limitation in COPD



only one of several structural abnormalities present in patients with COPD. Chronic bronchitis, or the presence of cough and sputum production for at least 3 months in each of two consecutive years, remains a clinically and epidemiologically useful term. However, it is important to recognize that chronic cough and sputum production (chronic bronchitis) is an independent disease entity that may precede or follow the development of airflow limitation and may be associated with development and/or acceleration of fixed airflow limitation. Chronic bronchitis also exists in patients with normal spirometry.

BURDEN OF COPD

COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing[2,5]. COPD prevalence, morbidity, and mortality vary across countries and across different groups within countries. COPD is the result of cumulative exposures over decades. Often, the prevalence of COPD is directly related to the prevalence of tobacco smoking, although in many countries, outdoor, occupational and indoor air pollution – the latter resulting from the burning of wood and other biomass fuels – are major COPD risk factors[6]. The prevalence and burden of COPD are projected to increase in the coming decades due to continued exposure to COPD risk factors and the changing age structure of the world's population (with more people living longer and therefore expressing the long-term effects of exposure to COPD risk factors)[5]. Information on the burden of COPD can be found on international

Websites such as those of the **World Health Organization (WHO)** *(http://www.who.int)* and the **World Bank/WHO Global Burden of Disease Study** *(http://www.who.int/topics/global_burden_of_disease).* Aging itself is a risk factor for COPD and aging of the airways and parenchyma mimic some of the structural changes associated with COPD[7].

Prevalence

Existing COPD prevalence data show remarkable variation due to differences in survey methods, diagnostic criteria, and analytic approaches[8]. The lowest estimates of prevalence are those based on self-reporting of a doctor diagnosis of COPD or equivalent condition. For example, most national data show that less than 6% of the adult population has been told that they have COPD[8]. This likely reflects the widespread under-recognition and under-diagnosis of COPD[9].

Despite the complexities, data are emerging that enable some conclusions to be drawn regarding COPD prevalence, not least because of increasing data quality control. A systematic review and meta-analysis of studies carried out in 28 countries between 1990 and 2004[8], and an additional study from Japan[10], provide evidence that the prevalence of COPD is appreciably higher in smokers and ex-smokers than in nonsmokers, in those over 40 years of age than those under 40, and in men than in women. The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO)[11] examined the prevalence of post-bronchodilator airflow limitation among persons over age 40 in five major Latin American cities, each in a different country – Brazil, Chile, Mexico, Uruguay, and Venezuela. In each country, the prevalence of COPD increased steeply with age, with the highest prevalence among those over age 60, ranging in the total population from a low of 7.8% in Mexico City, Mexico to a high of 19.7% in Montevideo, Uruguay. In all cities/countries the prevalence was appreciably higher in men than in women[11], which contrasts with findings from European cities such as Salzburg[12]. The Burden of Obstructive Lung Diseases program (BOLD) has carried out surveys in several parts of the world[13] and has documented more severe disease than previously found and a substantial prevalence (3-11%) of COPD among never-smokers.

Morbidity

Morbidity measures traditionally include physician visits, emergency department visits, and hospitalizations. Although COPD databases for these outcome parameters are less readily available and usually less reliable than mortality databases, the limited data available indicate that morbidity due to COPD increases with age[10-12]. Morbidity from COPD may be affected by other comorbid chronic conditions (e.g., cardiovascular disease, musculoskeletal impairment, diabetes mellitus) that are related to COPD and may have an impact on the patient's health status, as well as interfere with COPD management.

Mortality

The World Health Organization publishes mortality statistics for selected causes of death annually for all WHO regions; additional information is available from the **WHO Evidence for Health Policy Department** (*http://www.who.int/evidence*). Data must be interpreted cautiously, however, because of inconsistent use of terminology for COPD. In the 10th revision of the ICD, deaths from COPD or chronic airways obstruction are included in the broad category of "COPD and allied conditions" (ICD-10 codes J42-46).

Under-recognition and under-diagnosis of COPD still affect the accuracy of mortality data[14,15]. Although COPD is often a primary cause of death, it is more likely to be listed as a contributory cause of death or omitted from the death certificate entirely[16,504]. However, it is clear that COPD is one of the most important causes of death in most countries. The Global Burden of Disease Study projected that COPD, which ranked sixth as a cause of death in 1990, will become the third leading cause of death worldwide by 2020; a newer projection estimated COPD will be the fourth leading cause of death in 2030[5]. This increased mortality is mainly driven by the expanding epidemic of smoking, reduced mortality from other common causes of death (e.g. ischemic heart disease, infectious diseases), and aging of the world population.

Economic Burden

COPD is associated with significant economic burden. In the European Union, the total direct costs of respiratory disease are estimated to be about 6% of the total health care budget, with COPD accounting for 56% (38.6 billion Euros) of this cost of respiratory disease[17]. In the United States the estimated direct costs of COPD are $29.5 billion and the indirect costs $20.4 billion[18]. COPD exacerbations account for the greatest proportion of the total COPD burden on the health care system. Not surprisingly, there is a striking direct relationship between the severity of COPD and the cost of care, and the distribution of costs changes as the disease progresses. For example, hospitalization and ambulatory oxygen costs soar as COPD severity increases. Any estimate of direct medical expenditures for home care under-represents the true cost of home care to society, because it ignores the economic value of the care provided to those with COPD by family members.

In developing countries, direct medical costs may be less important than the impact of COPD on workplace and home productivity. Because the health care sector might not provide long-term supportive care services for severely disabled individuals, COPD may force two individuals to leave the workplace—the affected individual and a family member who must now stay home to care for the disabled relative. Since human capital is often the most important national asset for developing countries, the indirect costs of COPD may represent a serious threat to their economies.

Social Burden

Since mortality offers a limited perspective on the human burden of a disease, it is desirable to find other measures of disease burden that are consistent and measurable across nations. The authors of the Global Burden of Disease Study designed a method to estimate the fraction of mortality and disability attributable to major diseases and injuries using a composite measure of the burden of each health problem, the Disability-Adjusted Life Year (DALY)[2,19,20]. The DALYs for a specific condition are the sum of years lost because of premature mortality and years of life lived with disability, adjusted for the severity of disability. In 1990, COPD was the twelfth leading cause of DALYs lost in the world, responsible for 2.1% of the total. According to the projections, COPD will be the seventh leading cause of DALYs lost worldwide in 2030[5].

FACTORS THAT INFLUENCE DISEASE DEVELOPMENT AND PROGRESSION

Although cigarette smoking is the best-studied COPD risk factor, it is not the only one and there is consistent evidence from epidemiologic studies that nonsmokers may also develop chronic airflow limitation[21-24]. Much of the evidence concerning risk factors for COPD comes from cross-sectional epidemiological studies that identify associations rather than cause-and-effect relationships. Although several longitudinal studies of COPD have followed groups and populations for up to 20 years[25], none has monitored the progression of the disease through its entire course, or has included the pre-and perinatal periods which may be important in shaping an individual's future COPD risk. Thus, current understanding of risk factors for COPD is in many respects still incomplete.

COPD results from a gene-environment interaction. Among people with the same smoking history, not all will develop COPD due to differences in genetic predisposition to the disease, or in how long they live. Risk factors for COPD may also be related in more complex ways. For example, gender may influence whether a person takes up smoking or experiences certain occupational or environmental exposures; socioeconomic status may be linked to a child's birth weight (as it impacts on lung growth and development and in turn on susceptibility to develop the disease); and longer life expectancy will allow greater lifetime exposure to risk factors. Understanding the relationships and interactions among risk factors requires further investigation.

Genes

The genetic risk factor that is best documented is a severe hereditary deficiency of alpha-1 antitrypsin[26], a major circulating inhibitor of serine proteases. Although alpha-1 antitrypsin deficiency is relevant to only a small part of the world's population, it illustrates the interaction between genes and environmental exposures leading to COPD.

A significant familial risk of airflow limitation has been observed in smoking siblings of patients with severe COPD[27], suggesting that genetic together with environmental factors could influence this susceptibility. Single genes such as the gene encoding matrix metalloproteinase 12 (*MMP12*) have been related to decline in lung function[28]. Although several genome-wide association studies indicate a role of the gene for the alpha-nicotinic acetylcholine receptor as well as the hedge-hog interacting protein gene and possibly one or two others, there remains a discrepancy between findings from analyses of COPD and lung function as well as between genome-wide association study analyses and candidate gene analyses[29-33].

Age and Gender

Age is often listed as a risk factor for COPD. It is unclear if healthy aging as such leads to COPD or if age reflects the sum of cumulative exposures throughout life. In the past, most studies showed that COPD prevalence and mortality were greater among men than women but data from developed countries[18,34] show that the prevalence of the disease is now almost equal in men and women, probably reflecting the changing patterns of tobacco smoking. Some studies have even suggested that women are more susceptible to the effects of tobacco smoke than men[35-38].

Lung Growth and Development

Lung growth is related to processes occurring during gestation, birth, and exposures during childhood and adolescence[39,40]. Reduced maximal attained lung function (as measured by spirometry) may identify individuals who are at increased risk for the development of COPD[41]. Any factor that affects lung growth during gestation and childhood has the potential for increasing an individual's risk of developing COPD. For example, a large study and meta-analysis confirmed a positive association between birth weight and FEV_1 in adulthood[42], and several studies have found an effect of early childhood lung infections.

A study found that factors in early life termed "childhood disadvantage factors" were as important as heavy smoking in predicting lung function in early adult life[43].

Exposure to Particles

Across the world, cigarette smoking is the most commonly encountered risk factor for COPD. Cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in FEV_1, and a greater COPD mortality rate than nonsmokers[44]. Other types of tobacco (e.g., pipe, cigar, water pipe[45]) and marijuana[46] are also risk factors for COPD[47,48]. Passive exposure to cigarette smoke (also known as environmental tobacco smoke or ETS) may also contribute to respiratory symptoms[49] and COPD[50] by increasing the lung's total burden of inhaled particles and gases[51,52]. Smoking during pregnancy may also pose a risk for the fetus, by affecting lung growth and development in utero and possibly the priming of the immune system[53,54].

Occupational exposures, including organic and inorganic dusts and chemical agents and fumes, are an underappreciated risk factor for COPD[55-57]. An analysis of the large U.S. population-based NHANES III survey of almost 10,000 adults aged 30-75 years estimated the fraction of COPD attributable to work was 19.2% overall, and 31.1% among never-smokers[58]. These estimates are consistent with a statement published by the American Thoracic Society that concluded that occupational exposures account for 10-20% of either symptoms or functional impairment consistent with COPD[59]. The risk from occupational exposures in less regulated areas of the world is likely to be much higher than reported in studies from Europe and North America.

Wood, animal dung, crop residues, and coal, typically burned in open fires or poorly functioning stoves, may lead to very high levels of indoor air pollution. Evidence continues to grow that indoor pollution from biomass cooking and heating in poorly ventilated dwellings is an important risk factor for COPD[60-66]. Almost 3 billion people worldwide use biomass and coal as their main source of energy for cooking, heating, and other household needs, so the population at risk worldwide is very large[63,67].

High levels of urban air pollution are harmful to individuals with existing heart or lung disease. The role of outdoor air pollution in causing COPD is unclear, but appears to be small when compared with that of cigarette smoking. It has also been difficult to assess the effects of single pollutants in long-term exposure to atmospheric pollution. However, air pollution from fossil fuel combustion, primarily from motor vehicle emissions in cities, is associated with decrements of respiratory function[68]. The relative effects of short-term, high-peak exposures and long-term, low-level exposures are yet to be resolved.

Socioeconomic Status

Poverty is clearly a risk factor for COPD but the components of poverty that contribute to this are unclear. There is strong evidence that the risk of developing COPD is inversely related to socioeconomic status[69]. It is not clear, however, whether this pattern reflects exposures to indoor and outdoor air pollutants, crowding, poor nutrition, infections, or other factors that are related to low socioeconomic status.

Asthma/Bronchial Hyperreactivity

Asthma may be a risk factor for the development of COPD, although the evidence is not conclusive. In a report from a longitudinal cohort of the Tucson Epidemiological Study of Airway Obstructive Disease, adults with asthma were found to have a twelve-fold higher risk of acquiring COPD over time than those without asthma, after adjusting for smoking[70]. Another longitudinal study of people with asthma found that around 20% of subjects developed irreversible airflow limitation and reduced transfer coefficient[71], and in a longitudinal study self-reported asthma was associated with excess loss of FEV_1 in the general population[72]. In the European Community Respiratory Health Survey, bronchial hyperresponsiveness was second only to cigarette smoking as the leading risk factor for COPD, responsible for 15% of the population attributable risk (smoking had a population attributable risk of 39%)[73]. The pathology of chronic airflow limitation in asthmatic nonsmokers and non-asthmatic smokers is markedly different, suggesting that the two disease entities may remain different even when presenting with similarly reduced lung function[74]. However, clinically separating asthma from COPD may not be easy.

Bronchial hyperreactivity can exist without a clinical diagnosis of asthma and has been shown to be an independent predictor of COPD in population studies[75] as well as an indicator of risk of excess decline in lung function in patients with mild COPD[76].

Chronic Bronchitis

In the seminal study by Fletcher and coworkers, chronic bronchitis was not associated with decline in lung function[77]. However, subsequent studies have found an association between mucus hypersecretion and FEV_1 decline[78], and in younger adults who smoke the presence of chronic bronchitis is associated with an increased likelihood of developing COPD[79,80].

Infections

A history of severe childhood respiratory infection has been associated with reduced lung function and increased respiratory symptoms in adulthood[39,73]. Susceptibility to infections plays a role in exacerbations of COPD but the effect on the development of the disease is less clear. HIV infection has been shown to accelerate the onset of smoking-related emphysema[81]. Tuberculosis has been found to be a risk factor for COPD[82,83]. In addition, tuberculosis is both a differential diagnosis to COPD and a potential comorbidity[83,84].

PATHOLOGY, PATHOGENESIS AND PATHOPHYSIOLOGY

Inhaled cigarette smoke and other noxious particles such as smoke from biomass fuels cause lung inflammation, a normal response that appears to be modified in patients who develop COPD. This chronic inflammatory response may induce parenchymal tissue destruction (resulting in emphysema), and disrupt normal repair and defense mechanisms (resulting in small airway fibrosis). These pathological changes lead to air trapping and progressive airflow limitation. A brief overview follows of the pathologic changes in COPD, their cellular and molecular mechanisms, and how these underlie physiologic abnormalities and symptoms characteristic of the disease[85]

Pathology

Pathological changes characteristic of COPD are found in the airways, lung parenchyma, and pulmonary vasculature[86]. The pathological changes include chronic inflammation, with increased numbers of specific inflammatory cell types in different parts of the lung, and structural changes resulting from repeated injury and repair. In general, the inflammatory and structural changes in the airways increase with disease severity and persist on smoking cessation.

Pathogenesis

The inflammation in the respiratory tract of COPD patients appears to be a modification of the inflammatory response of the respiratory tract to chronic irritants such as cigarette smoke. The mechanisms for this amplified inflammation are not yet understood but may be genetically determined. Patients can clearly develop COPD without smoking, but the nature of the inflammatory response in these patients is unknown. Oxidative stress and an excess of proteinases in the lung further modify lung inflammation. Together, these mechanisms lead to the characteristic pathological changes in COPD. Lung inflammation persists after smoking cessation through unknown mechanisms, although autoantigens and persistent microorganisms may play a role[87].

Oxidative Stress. Oxidative stress may be an important amplifying mechanism in COPD[88]. Biomarkers of oxidative stress (e.g., hydrogen peroxide, 8-isoprostane) are increased in the exhaled breath condensate, sputum, and systemic circulation of COPD patients. Oxidative stress is further increased in exacerbations. Oxidants are generated by cigarette smoke and other inhaled particulates, and released from activated inflammatory cells such as macrophages and neutrophils. There may also be a reduction in endogenous antioxidants in COPD patients as a result of reduction in a transcription factor called Nrf2 that regulates many antioxidant genes[89].

Protease-Antiprotease Imbalance. There is compelling evidence for an imbalance in the lungs of COPD patients between proteases that break down connective tissue components and antiproteases that protect against this. Several proteases, derived from inflammatory cells and epithelial cells, are increased in COPD patients. There is increasing evidence that they may interact with each other. Protease-mediated destruction of elastin, a major connective tissue component in lung parenchyma, is believed to be an important feature of emphysema and is likely to be irreversible.

Inflammatory Cells. COPD is characterized by a specific pattern of inflammation involving increased numbers of CD8+ (cytotoxic) Tc1 lymphocytes present only in smokers that develop the disease[85]. These cells, together with neutrophils and macrophages, release inflammatory mediators and enzymes and interact with structural cells in the airways, lung parenchyma and pulmonary vasculature[90].

Inflammatory Mediators. The wide variety of inflammatory mediators that have been shown to be increased in COPD patients[91] attract inflammatory cells from the circulation (chemotactic factors), amplify the inflammatory process (proinflammatory cytokines), and induce structural changes (growth factors)[92].

Differences in Inflammation Between COPD and Asthma. Although both COPD and asthma are associated with chronic inflammation of the respiratory tract, there are differences in the inflammatory cells and mediators involved in the two diseases, which in turn account for differences in physiological effects, symptoms, and response to therapy[74]. Some patients with COPD have features consistent with asthma and may have a mixed inflammatory pattern with increased eosinophils.

Pathophysiology

There is now a good understanding of how the underlying disease process in COPD leads to the characteristic physiologic abnormalities and symptoms. For example, inflammation and narrowing of peripheral airways leads to decreased FEV_1. Parenchymal destruction due to emphysema also contributes to airflow limitation and leads to decreased gas transfer.

Airflow Limitation and Air Trapping. The extent of inflammation, fibrosis, and luminal exudates in small airways is correlated with the reduction in FEV_1 and FEV_1/FVC ratio, and probably with the accelerated decline in FEV_1 characteristic of COPD[90]. This peripheral airway obstruction progressively traps air during expiration, resulting in hyperinflation. Although emphysema is more associated with gas exchange abnormalities than with reduced FEV_1, it does contribute to gas trapping during expiration. This is especially so as alveolar attachments to small airways are destroyed when the disease becomes more severe. Hyperinflation reduces inspiratory capacity such that functional residual capacity increases, particularly during exercise (dynamic hyperinflation), resulting in increased dyspnea and limitation of exercise capacity. These factors contribute to impairment of the intrinsic contractile properties of respiratory muscles; this results in upregulation of local pro-inflammatory cytokines. It is thought that hyperinflation develops early in the disease and is the main mechanism for exertional dyspnea[93,94]. Bronchodilators acting on peripheral airways reduce air trapping, thereby reducing lung volumes and improving symptoms and exercise capacity[93].

Gas Exchange Abnormalities. Gas exchange abnormalities result in hypoxemia and hypercapnia, and have several mechanisms in COPD. In general, gas transfer for oxygen and carbon dioxide worsens as the disease progresses. Reduced ventilation may also be due to reduced ventilatory drive. This may lead to carbon dioxide retention when it is combined with reduced ventilation due to a high work of breathing because of severe obstruction and hyperinflation coupled with ventilatory muscle impairment. The abnormalities in alveolar ventilation and a reduced pulmonary vascular bed further worsen the V_A/Q abnormalities[95].

Mucus Hypersecretion. Mucus hypersecretion, resulting in a chronic productive cough, is a feature of chronic bronchitis and is not necessarily associated with airflow limitation. Conversely, not all patients with COPD have symptomatic mucus hypersecretion. When present, it is due to an increased number of goblet cells and enlarged submucosal glands in response to chronic airway irritation by cigarette smoke and other noxious agents. Several mediators and proteases stimulate mucus hypersecretion and many of them exert their effects through the activation of epidermal growth factor receptor (EGFR)[96].

Pulmonary Hypertension. Pulmonary hypertension may develop late in the course of COPD and is due mainly to hypoxic vasoconstriction of small pulmonary arteries, eventually resulting in structural changes that include intimal hyperplasia and later smooth muscle hypertrophy/hyperplasia[97]. There is an inflammatory response in vessels similar to that seen in the airways and evidence of endothelial cell dysfunction. The loss of the pulmonary capillary bed in emphysema may also contribute to increased pressure in the pulmonary circulation. Progressive pulmonary hypertension may lead to right ventricular hypertrophy and eventually to right-side cardiac failure.

Exacerbations. Exacerbations of respiratory symptoms often occur in patients with COPD, triggered by infection with bacteria or viruses (which may coexist), environmental pollutants, or unknown factors. Patients with bacterial and viral episodes have a characteristic response with increased inflammation. During respiratory exacerbations there is increased hyperinflation and gas trapping, with reduced expiratory flow, thus accounting for the increased dyspnea[98]. There is also worsening of V_A/Q abnormalities, which can result in hypoxemia[99]. Other conditions (pneumonia, thromboembolism, and acute cardiac failure) may mimic or aggravate an exacerbation of COPD.

Systemic Features. It is increasingly recognized that many patients with COPD have comorbidities that have a major impact on quality of life and survival[100]. Airflow limitation and particularly hyperinflation affect cardiac function and gas exchange[101]. Inflammatory mediators in the circulation may contribute to skeletal muscle wasting and cachexia, and may initiate or worsen comorbidities such as ischemic heart disease, heart failure, osteoporosis, normocytic anemia, diabetes, metabolic syndrome, and depression.

CHAPTER

2

DIAGNOSIS AND ASSESSMENT

CHAPTER 2: DIAGNOSIS AND ASSESSMENT

KEY POINTS:

- A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for the disease.
- Spirometry is required to make the diagnosis in this clinical context; the presence of a post-bronchodilator FEV_1/FVC < 0.70 confirms the presence of persistent airflow limitation and thus of COPD.
- The goals of COPD assessment are to determine the severity of the disease, including the severity of airflow limitation, the impact on the patient's health status, and the risk of future events (such as exacerbations, hospital admissions, or death), in order to guide therapy.
- Comorbidities occur frequently in COPD patients, including cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, and lung cancer. Given that they can occur in patients with mild, moderate and severe airflow limitation and influence mortality and hospitalizations independently, comorbidities should be actively looked for, and treated appropriately if present.

DIAGNOSIS

A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for the disease (**Table 2.1**). Spirometry is required to make the diagnosis in this clinical context[505]; the presence of a post-bronchodilator FEV_1/FVC < 0.70 confirms the presence of persistent airflow limitation and thus of COPD.

The spirometric criterion for airflow limitation remains a post-bronchodilator fixed ratio of FEV_1/FVC < 0.70. This criterion is simple, independent of reference values, and has been used in numerous clinical trials forming the evidence base from which most of our treatment recommendations are drawn. Diagnostic simplicity and consistency are key for the busy non-specialist clinician.

While post-bronchodilator spirometry is required for the diagnosis and assessment of severity of COPD, the degree of reversibility of airflow limitation (e.g., measuring FEV_1 before and after bronchodilator or corticosteroids) is no longer recommended[506]. The degree of reversibility has never been shown to add to the diagnosis, differential diagnosis with asthma, or to predicting the response to long-term treatment with bronchodilators or corticosteroids.

Table 2.1. Key Indicators for Considering a Diagnosis of COPD

Consider COPD, and perform spirometry, if any of these indicators are present in an individual over age 40. These indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is required to establish a diagnosis of COPD.

Dyspnea that is:	Progressive (worsens over time). Characteristically worse with exercise. Persistent.
Chronic cough:	May be intermittent and may be unproductive.
Chronic sputum production:	Any pattern of chronic sputum production may indicate COPD.
History of exposure to risk factors:	Tobacco smoke (including popular local preparations). Smoke from home cooking and heating fuels. Occupational dusts and chemicals.
Family history of COPD	

The role of screening spirometry in the general population is controversial. Both FEV_1 and FVC predict all-cause mortality independent of tobacco smoking, and abnormal lung function identifies a subgroup of smokers at increased risk for lung cancer. This has been the basis of an argument that screening spirometry should be employed as a global health assessment tool[102,103]. However, there are no data to indicate that screening spirometry is effective in directing management decisions or in improving COPD outcomes in patients who are identified before the development of significant symptoms[104]. Thus, GOLD advocates active case finding but not screening spirometry.

The use of the fixed FEV_1/FVC ratio to define airflow limitation will result in more frequent diagnosis of COPD in the elderly[105], and less frequent diagnosis in adults younger than 45 years[106], especially of mild disease, compared to using a cutoff based on the lower limit of normal (LLN) values for FEV_1/FVC. These LLN values are based on the normal distribution and classify the bottom 5% of the healthy population as abnormal. From a scientific perspective it is difficult to determine which of these criteria is correct to diagnose COPD[107], and no studies exist comparing clinical diagnosis based on the two approaches. However, LLN values are highly dependent on the choice of valid reference equations using post-bronchodilator FEV_1, and neither longitudinal studies validating the use of the LLN nor studies using reference equations in populations where smoking is not the major cause of COPD are available. The risk of misdiagnosis and over-treatment of individual patients using the fixed ratio as a diagnostic criterion is limited, as spirometry is only one parameter for establishing the clinical diagnosis of COPD, the others being symptoms and risk factors.

Symptoms

The characteristic symptoms of COPD are chronic and progressive dyspnea, cough, and sputum production that can be variable from day-to-day[507,508]. Chronic cough and sputum production may precede the development of airflow limitation by many years. Individuals, particularly those exposed to COPD risk factors, who present with these symptoms should be examined to search for an underlying cause(s) and appropriate interventions taken. Conversely, significant airflow limitation may develop without chronic cough and sputum production. Although COPD is defined on the basis of airflow limitation, in practice the decision to seek medical help (and so permit the diagnosis to be made) is usually determined by the impact of a symptom on a patient's daily life. A person may seek medical attention either because of chronic symptoms or because of a first exacerbation.

Dyspnea. Dyspnea, a cardinal symptom of COPD, is a major cause of disability and anxiety associated with the disease. Typical COPD patients describe their dyspnea as a sense of increased effort to breathe, heaviness, air hunger, or gasping[108]. However, the terms used to describe dyspnea vary both by individual and by culture[109].

Cough. Chronic cough, often the first symptom of COPD to develop[110], is frequently discounted by the patient as an expected consequence of smoking and/or environmental exposures. Initially, the cough may be intermittent, but later is present every day, often throughout the day. The chronic cough in COPD may be unproductive[111]. In some cases, significant airflow limitation may develop without the presence of a cough. **Table 2.2** lists some of the other causes of chronic cough.

Sputum production. COPD patients commonly raise small quantities of tenacious sputum after coughing bouts. Regular production of sputum for 3 or more months in 2 consecutive years (in the absence of any other conditions that may explain it) is the epidemiological definition of chronic bronchitis[112], but this is a somewhat arbitrary definition that does not reflect the range of sputum production in COPD patients. Sputum production is often difficult to evaluate because patients may swallow sputum rather than expectorate it, a habit subject to significant cultural and gender variation. Patients producing large volumes of sputum may have underlying bronchiectasis. The presence of purulent sputum reflects an increase in inflammatory mediators[113], and its development may identify the onset of a bacterial exacerbation[114].

Table 2.2. Causes of Chronic Cough
Intrathoracic
• *Chronic obstructive pulmonary disease*
• *Asthma*
• *Lung cancer*
• *Tuberculosis*
• *Bronchiectasis*
• *Left heart failure*
• *Interstitial lung disease*
• *Cystic fibrosis*
• *Idiopathic cough*
Extrathoracic
• *Chronic allergic rhinitis*
• *Upper Airway Cough Syndrome (UACS)*
• *Gastroesophageal reflux*
• *Medication (e.g., ACE inhibitors)*

Wheezing and Chest Tightness. Wheezing and chest tightness are nonspecific symptoms that may vary between days, and over the course of a single day. Audible wheeze may arise at a laryngeal level and need not be accompanied by auscultatory abnormalities. Alternatively, widespread inspiratory or expiratory wheezes can be present on listening to the chest. Chest tightness often follows exertion, is poorly localized, is muscular in character, and may arise from isometric contraction of the intercostal muscles. An absence of wheezing or chest tightness does not exclude a diagnosis of COPD, nor does the presence of these sypmtoms confirm a diagnosis of asthma.

Additional Features in Severe Disease. Fatigue, weight loss and anorexia are common problems in patients with severe and very severe COPD[115]. They are prognostically important[116] and can also be a sign of other diseases (e.g., tuberculosis, lung cancer), and therefore should always be investigated. Cough syncope occurs due to rapid increases in intrathoracic pressure during prolonged attacks of coughing. Coughing spells may also cause rib fractures, which are sometimes asymptomatic. Ankle swelling may be the only symptomatic pointer to the development of cor pulmonale. Symptoms of depression and/or anxiety merit specific enquiry in the clinical history because they are common in COPD[117] and are associated with increased risk of exacerbations and poorer health status.

Medical History

A detailed medical history of a new patient known or thought to have COPD should assess:

- *Patient's exposure to risk factors*, such as smoking and occupational or environmental exposures
- *Past medical history*, including asthma, allergy, sinusitis, or nasal polyps; respiratory infections in childhood; other respiratory diseases
- *Family history of COPD or other chronic respiratory disease*
- *Pattern of symptom development*: COPD typically develops in adult life and most patients are conscious of increased breathlessness, more frequent or prolonged "winter colds," and some social restriction for a number of years before seeking medical help
- *History of exacerbations or previous hospitalizations for respiratory disorder:* Patients may be aware of periodic worsening of symptoms even if these episodes have not been identified as exacerbations of COPD
- *Presence of comorbiditie*s, such as heart disease, osteoporosis, musculoskeletal disorders, and malignancies that may also contribute to restriction of activity[118]
- *Impact of disease on patient's life*, including limitation of activity, missed work and economic impact, effect on family routines, feelings of depression or anxiety, well being and sexual activity
- *Social and family support available to the patient*
- *Possibilities for reducing risk factors, especially smoking cessation*

Physical Examination

Although an important part of patient care, a physical examination is rarely diagnostic in COPD. Physical signs of airflow limitation are usually not present until significant impairment of lung function has occurred[119,120], and their detection has a relatively low sensitivity and specificity. A number of physical signs may be present in COPD, but their absence does not exclude the diagnosis.

Spirometry

Spirometry is the most reproducible and objective measurement of airflow limitation available. Peak expiratory flow measurement alone cannot be reliably used as the only diagnostic test, despite its good sensitivity, because of its weak specificity[121]. Good quality spirometric measurement is possible in any health care setting and all health care workers who care for COPD patients should have access to spirometry. **Table 2.3** summarizes some of the factors needed to achieve accurate test results.

Spirometry should measure the volume of air forcibly exhaled from the point of maximal inspiration (forced vital capacity, FVC) and the volume of air exhaled during the first second of this maneuver (forced expiratory volume in one second, FEV_1), and the ratio of these two measurements (FEV_1/FVC) should be calculated. The ratio between FEV_1 and slow vital capacity (VC), FEV_1/VC, is sometimes measured instead of the FEV_1/FVC ratio. This will often lead to lower values of the ratio, especially in pronounced airflow limitation; however, the cut-off point of 0.7 should still be applied. Spirometry measurements are evaluated by comparison with reference values[122] based on age, height, sex, and race.

Table 2.3. Considerations in Performing Spirometry
Preparation • Spirometers need calibration on a regular basis. • Spirometers should produce hard copy or have a digital display of the expiratory curve to permit detection of technical errors or have an automatic prompt to identify an unsatisfactory test and the reason for it. • The supervisor of the test needs training in its effective performance. • Maximal patient effort in performing the test is required to avoid underestimation of values and hence errors in diagnosis and management.
Bronchodilation • Possible dosage protocols are 400 mcg $beta_2$-agonist, 160 mcg anticholinergic, or the two combined[122]. FEV_1 should be measured 10-15 minutes after a short-acting $beta_2$-agonist is given, or 30-45 minutes after a short-acting anticholinergic or a combination.
Performance • Spirometry should be performed using techniques that meet published standards[123]. • The expiratory volume/time traces should be smooth and free from irregularities. • The recording should go on long enough for a volume plateau to be reached, which may take more than 15 seconds in severe disease. • Both FVC and FEV_1 should be the largest value obtained from any of 3 technically satisfactory curves and the FVC and FEV_1 values in these three curves should vary by no more than 5% or 150 ml, whichever is greater. • The FEV_1/FVC ratio should be taken from the technically acceptable curve with the largest sum of FVC and FEV_1.
Evaluation • Spirometry measurements are evaluated by comparison of the results with appropriate reference values based on age, height, sex, and race. • The presence of a postbronchodilator FEV_1/FVC < 0.70 confirms the presence of airflow limitation.

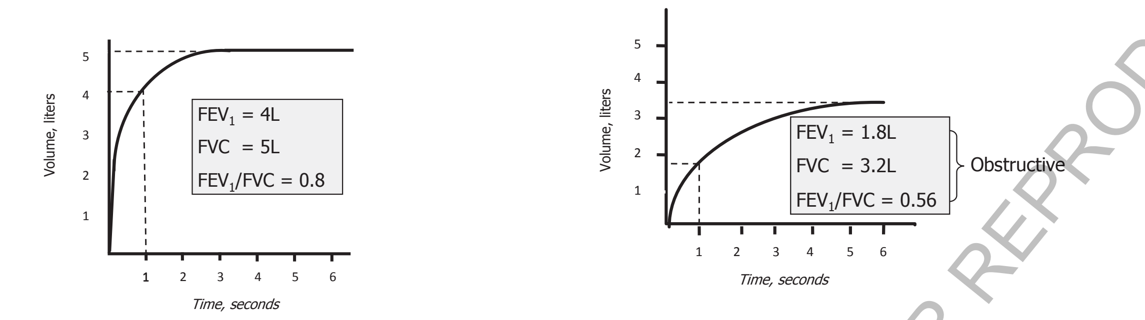
Figure 2.1A shows a normal spirometry tracing; **Figure 2.1B** a spirometry tracing typical of a patient with obstructive disease. Patients with COPD typically show a decrease in both FEV_1 and FVC.

ASSESSMENT OF DISEASE

The goals of COPD assessment are to determine the severity of the disease, its impact on the patient's health status and the risk of future events (such as exacerbations, hospital admissions or death), in order to, eventually, guide therapy.

Figure 2.1A. Spirometry - Normal Trace

Figure 2.1B. Spirometry - Obstructive Disease



To achieve these goals, COPD assessment must consider the following aspects of the disease separately:

- Current level of patient's symptoms
- Severity of the spirometric abnormality
- Exacerbation risk
- Presence of comorbidities

Assessment of Symptoms

In the past, COPD was viewed as a disease largely characterized by breathlessness. A simple measure of breathlessness such as the Modified British Medical Research Council (mMRC) Questionnaire (**Table 2.4**) was considered adequate for assessment of symptoms, as the mMRC relates well to other measures of health status[91] and predicts future mortality risk[92]. However, it is now recognized that COPD has multiple symptomatic effects[151]. For this reason, a comprehensive symptom assessment is recommended rather than just a measure of breathlessness.

The most comprehensive disease-specific health-related quality of life or health status questionnaires such as the CRQ[236] and SGRQ[347] are too complex to use in routine practice, but two shorter comprehensive measures (COPD Assessment Test, CAT and COPD Control Questionnaire, CCQ) have been developed and are suitable.

COPD Assessment Test (CAT). The COPD Assessment Test is an 8-item unidimensional measure of health status impairment in COPD[124]. It was developed to be applicable worldwide and validated translations are available in a wide range of languages. The score ranges from 0-40, correlates very closely with the SGRQ, and has been extensively documented in numerous publications[548] (http://www.catestonline.org).

COPD Control Questionnaire (CCQ). The COPD Control Questionnaire is a 10 item self-administered questionnaire developed to measure clinical control in patients with

Table 2.4. Modified Medical Research Council Questionnaire for Assessing the Severity of Breathlessness

PLEASE TICK IN THE BOX THAT APPLIES TO YOU (ONE BOX ONLY)	
mMRC Grade 0. I only get breathless with strenuous exercise.	☐
mMRC Grade 1. I get short of breath when hurrying on the level or walking up a slight hill.	☐
mMRC Grade 2. I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	☐
mMRC Grade 3. I stop for breath after walking about 100 meters or after a few minutes on the level.	☐
mMRC Grade 4. I am too breathless to leave the house or I am breathless when dressing or undressing.	☐

COPD[509, 510]. Although the concept of "control" in COPD remains controversial, the CCQ is short and easy to administer. It is reliable and responsive, is available in a range of languages, and has been validated (http://www.ccq.nl).

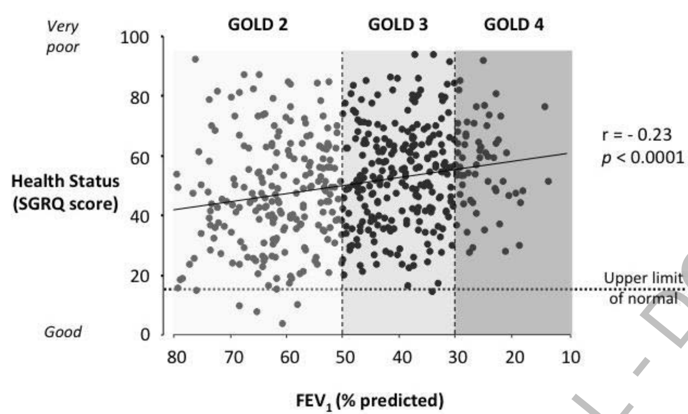
Choice of Cut Points

The CAT and CCQ provide a measure of the symptomatic impact of COPD but do not categorize patients into lower and higher symptoms for the purpose of treatment. The SGRQ is the most widely documented comprehensive measure; scores less than 25 are uncommon in diagnosed COPD patients[131,549] and scores ≥ 25 are very uncommon in healthy persons[549]. In clinical trials of long-acting bronchodilator medications [201,210, 516, 550-553], the baseline weighted mean SGRQ score was 44, and one standard deviation below the mean was 26. Therefore, it is

Table 2.5. Classification of Severity of Airflow Limitation in COPD (Based on Post-Bronchodilator FEV_1)

In patients with $FEV_1/FVC < 0.70$:		
GOLD 1:	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2:	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3:	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4:	Very Severe	$FEV_1 < 30\%$ predicted

Figure 2.2. Relationship Between Health-related Quality of Life, Post-bronchodilator FEV_1 and GOLD Spirometric Classification (Adapted from Jones[127])



recommended that a symptom score equivalent to SGRQ score ≥ 25 should be used as the cut-point for considering regular treatment for symptoms including breathlessness, particularly since this corresponds to the range of severity seen in patients recruited to the trials that provide the evidence base for treatment recommendations. The equivalent cut-point for the CAT is 10[123, 554]. The equivalent cut-point for the CCQ has yet to be finally determined, but appears to be in the range 1.0 - 1.5.

An equivalent mMRC score cannot be calculated because a simple breathlessness cut-point cannot equate to a comprehensive symptom score cut-point. The great majority of patients with an SGRQ of 25 or more will have an mMRC of 2 or more; however patients with mMRC < 2 may also have a number of other COPD symptoms. While use of an mMRC ≥ 2 as a cut-point may be adequate for breathlessness assessment, it will also categorize a number of patients with symptoms other than breathlessness as having "few symptoms." For this reason, the use of a comprehensive symptom assessment is recommended. However, because use of the mMRC is still widespread, an mMRC of ≥ 2 is still included as a cut-point for separating "less breathlessness" from "more breathlessness." However, users are cautioned that assessment of other symptoms is required[554,555].

Spirometric Assessment

Table 2.5 shows the classification of airflow limitation severity in COPD. Specific spirometric cut-points are used for purposes of simplicity. Spirometry should be performed after the administration of an adequate dose of a short-acting inhaled bronchodilator in order to minimize variability.

However, there is only a weak correlation between FEV_1, symptoms and impairment of a patient's health-related quality of life. This is illustrated in **Figure 2.2** in which health-related quality of life is plotted against post-bronchodilator FEV_1[126,127] with the GOLD spirometric classification superimposed. The figure illustrates that, within any given category, patients may have anything between relatively well preserved to very poor health status. For this reason, formal symptomatic assessment is also required.

Assessment of Exacerbation Risk

An exacerbation of COPD is defined as an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication[128-130]. The rate at which exacerbations occur varies greatly between patients[131,512]. The best predictor of having frequent exacerbations (2 or more exacerbations per year) is a history of previous treated events[132]. In addition, worsening airflow limitation is associated with an increasing prevalence of exacerbations and risk of death. Hospitalization for a COPD exacerbation is associated with a poor prognosis with increased risk of death[556].

A large body of data has been accumulated in patients[131,152] classified using GOLD spirometric grading systems. These show an increase in risk of exacerbations, hospitalization and death with worsening of airflow limitation. The data in **Table 2.6** are derived from prospectively collected data from large medium-term clinical trials[132-134]. They are not precise estimates that apply to each patient, but they illustrate clearly the increased risk of exacerbations and death between spirometric levels. Roughly, although up to 20% of GOLD 2 (Moderate aiflow limitation) patients may experience frequent exacerbations requiring treatment with antibiotics and/or systemic corticosteroids[132], the risk of exacerbations significantly increases in GOLD 3 (Severe) and GOLD 4 (Very Severe). Since exacerbations increase the decline in lung function, deterioration in health status and risk of death, the assessment of exacerbation risk can also be seen as an assessment of the risk of poor outcomes in general.

Table 2.6: RISK IN COPD: Placebo-limb data from TORCH[134*], Uplift[133†] and Eclipse[132 ≠]

GOLD spirometric level	Exacerbations (per year)*†≠	Hospitalizations (per year)* ≠	3-year Mortality*†
GOLD 1: Mild	?	?	?
GOLD 2: Moderate	0.7 – 0.9	0.11 – 0.2	11%*†
GOLD 3: Severe	1.1 – 1.3	0.25 – 0.3	15%*
GOLD 4: Very severe	1.2 – 2.0	0.4 – 0.54	24%*

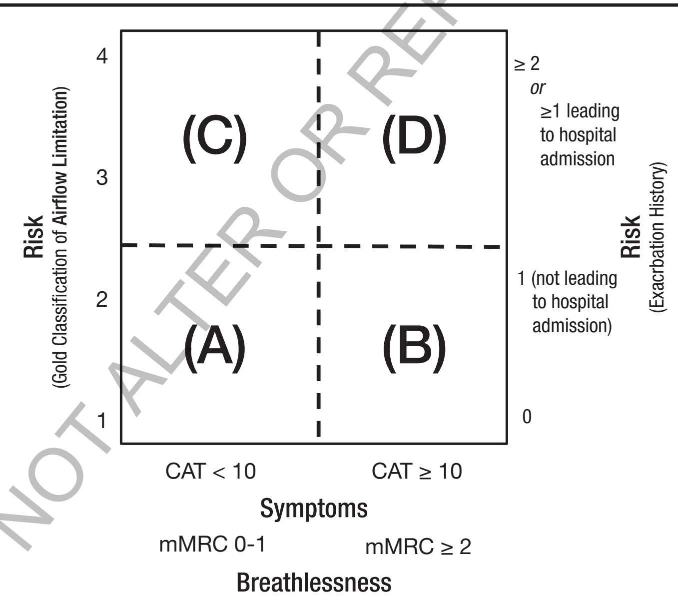
*Toward a Revolution in COPD Health (TORCH) study[134]
† Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study[133]
≠ Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study[132]

Assessment of Comorbidities

Because COPD often develops in long-time smokers in middle age, patients frequently have a variety of other diseases related to either smoking or aging[135]. COPD itself also has significant extrapulmonary (systemic) effects including weight loss, nutritional abnormalities and skeletal muscle dysfunction. The latter is characterized by both sarcopenia (loss of muscle cells) and abnormal function of the remaining cells136. Its causes are likely multifactorial (inactivity, poor diet, inflammation, hypoxia) and it can contribute to exercise intolerance and poor health status in patients with COPD. Importantly, skeletal muscle dysfunction is a remediable source of exercise intolerance[137].

Comorbidities that occur frequently in COPD patients include cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression and lung cancer. The existence of COPD may actually increase the risk for other diseases; this is particularly striking for COPD and lung cancer[138-141]. Whether this association is due to common risk factors (e.g., smoking), involvement of susceptibility genes, or impaired clearance of carcinogens is not clear. Comorbidities can occur in patients with mild, moderate or severe airflow limitation[131], influence mortality and hospitalizations independently[142], and deserve specific treatment. Therefore, comorbidities should be looked for routinely, and treated appropriately, in any patient with COPD. The guidelines for the diagnosis, assessment of severity, and management of individual comorbidities in patients with COPD are the same as for all other patients. A more detailed description of the management of COPD and comorbidities is given in Chapter 6.

Figure 2.3. Assessment Using Symptoms, Breathlessness, Spirometric Classification and Risk of Exacerbations



Combined COPD Assessment

An understanding of the impact of COPD on an individual patient combines the symptomatic assessment with the patient's spirometric classification and/or risk of exacerbations. This approach to combined assessment is illustrated in **Figure 2.3**.

As detailed above, the CAT is recommended as a comprehensive measure of symptoms, with a CAT score ≥ 10 indicating a high level of symptoms. Comprehensive assessment of the symptomatic impact of the disease is preferred, but in its absence mMRC scores provide an assessment of the impact of dyspnea. It is unnecessary and possibly confusing to use more than one scale.

There are three methods of assessing exacerbation risk. One is a population-based method using the GOLD spirometric classification (**Table 2.5**), with GOLD 3 or GOLD 4 categories indicating high risk. The second based on the individual patient's history of exacerbations[132], with two or more exacerbations in the preceding year indicating high risk. The third is a history of hospitalization due to an exacerbation in the preceding year. (If there is a discrepancy between these criteria, the assessment pointing to the highest risk should be used.) To use **Figure**

2.3, first assess symptoms with the CAT scale (or dyspnea with the mMRC) and determine if the patient belongs to the boxes on the left side – Less Symptoms (CAT < 10) or Less Breathlessness (mMRC grade 0-1); or belongs to boxes on the right side - More Symptoms (CAT ≥ 10) or More Breathlessness (mMRC grade ≥ 2).

Next assess the risk of exacerbations to determine if the patient belongs to the lower part of the box – Low Risk – or the upper part of the box – High Risk. This can be done by one of three methods: (1) use spirometry to determine the GOLD grade of airflow limitation (GOLD 1 and GOLD 2 categories indicate Low Risk, while GOLD 3 and GOLD 4 indicate High Risk); (2) assess the number of exacerbations the patient has had within the previous 12 months (0 or 1 indicates Low Risk, while 2 or more exacerbations indicates High Risk); (3) determine whether the patient has had one or more hospitalization in the previous year for a COPD exacerbation. In some patients, these three ways of assessing risk of exacerbations will not lead to the same level of risk; in this case, the risk should be determined by the method indicating High Risk.

Example: Imagine a patient with a CAT score of 18, FEV_1 of 55% of predicted, and a history of 3 exacerbations within the last 12 months. Symptom assessment using CAT shows that the patient is More Symptomatic (CAT ≥ 10) and is therefore either Group B or Group D. Spirometry indicates Low Risk as the patient is GOLD 2 (Moderate airflow limitation) but as the patient had 3 exacerbations within the last 12 months this indicates High Risk and outweighs the lower risk assessment based on spirometry. The patient therefore belongs in Group D.

The groups can be summarized as follows:

- **Patient Group A – Low Risk, Less Symptoms** Typically GOLD 1 or GOLD 2 (Mild or Moderate airflow limitation); and/or 0-1 exacerbation per year *and* no hospitalization for exacerbation; *and* CAT score < 10 *or* mMRC grade 0-1

- **Patient Group B – Low Risk, More Symptoms** Typically GOLD 1 or GOLD 2 (Mild or Moderate airflow limitation); and/or 0-1 exacerbation per year *and* no hospitalization for exacerbation; *and* CAT score ≥ 10 *or* mMRC grade ≥ 2

- **Patient Group C – High Risk, Less Symptoms** Typically GOLD 3 or GOLD 4 (Severe or Very Severe airflow limitation); and/or ≥ 2 exacerbations per year *or* ≥ 1 with hospitalization for exacerbation; *and* CAT score < 10 *or* mMRC grade 0-1

- **Patient Group D – High Risk, More Symptoms** Typically GOLD 3 or GOLD 4 (Severe or Very Severe airflow limitation); and/or ≥ 2 exacerbations per year *or* ≥ 1 with hospitalization for exacerbation; *and* CAT score ≥ 10 *or* mMRC grade ≥ 2

Evidence to support this classification system includes:

- Patients with a high risk of exacerbations tend to be in GOLD categories 3 and 4 (Severe or Very Severe airflow limitation, **Figure 2.3**) and can be identified quite reliably from the their own past history[132].
- Higher exacerbation rates are associated with faster loss of FEV_1[143] and greater worsening of health status[144].
- Hospitalization for a COPD exacerbation is associated with a poor prognosis[556].
- CAT scores ≥ 10 are associated with significantly impaired health status[145].

Even in the absence of frequent exacerbations, patients in GOLD categories 3 and 4 may be at greater risk of hospital admission and death (**Figure 2.3**). These important increased risks form the rationale for including such patients in the "High Risk" groups.

This approach, combined with an assessment of potential comorbidities, reflects the complexity of COPD better than the unidimensional analysis of airflow limitation previously used for staging the disease and forms the basis of the guide to individualized management provided in Chapter 4.

Additional Investigations

The following additional investigations may be considered as part of the diagnosis and assessment of COPD:

Imaging. A chest X-ray is not useful to establish a diagnosis in COPD, but it is valuable in excluding alternative diagnoses and establishing the presence of significant comorbidities such as concomitant respiratory (pulmonary fibrosis, bronchiectasis, pleural diseases), skeletal (e.g., kyphoscoliosis), and cardiac diseases (e.g., cardiomegaly). Radiological changes associated with COPD include signs of lung hyperinflation (flattened diaphragm on the lateral chest film, and an increase in the volume of the retrosternal air space), hyperlucency of the lungs, and rapid tapering of the vascular markings. Computed tomography (CT) of the chest is not routinely recommended. However, when there is doubt about the diagnosis of COPD, CT scanning might help in the differential diagnosis where concomitant diseases are present. In addition, if a surgical procedure such as lung volume reduction is contemplated, a chest CT scan is necessary since the distribution of emphysema is one of the most important determinants of surgical suitability[146].

Lung Volumes and Diffusing Capacity. COPD patients exhibit gas trapping (a rise in residual volume) from early in the disease, and as airflow limitation worsens static hyperinflation (an increase in total lung capacity) occurs. These changes can be documented by body plethysmography, or less accurately by helium dilution lung volume measurement. These measurements help characterize the severity of COPD but are not essential to patient management. Measurement of diffusing capacity (DL_{CO}) provides information on the functional impact of emphysema in COPD and is often helpful in patients with breathlessness that may seem out of proportion with the degree of airflow limitation.

Oximetry and Arterial Blood Gas Measurement. Pulse oximetry can be used to evaluate a patient's oxygen saturation and need for supplemental oxygen therapy. Pulse oximetry should be used to assess all stable patients with FEV_1 < 35% predicted or with clinical signs suggestive of respiratory failure or right heart failure. If peripheral saturation is < 92% arterial blood gases should be assessed[147].

Alpha-1 Antitrypsin Deficiency Screening. The World Health Organization recommends that COPD patients from areas with a particularly high prevalence of alpha-1 antitrypsin deficiency should be screened for this genetic disorder[148]. However, the typical patient tends to present at a younger age (< 45 years) with lower lobe emphysema. Family members can be identified and family screening is useful for appropriate counseling. A serum concentration of alpha-1 antitrypsin below 15-20% of the normal value is highly suggestive of homozygous alpha-1 antitrypsin deficiency.

Exercise Testing. Objectively measured exercise impairment, assessed by a reduction in self-paced walking distance[149] or during incremental exercise testing in a laboratory[150], is a powerful indicator of health status impairment and predictor of prognosis[151]; exercise capacity may fall in the year before death[557]. Walking tests can be useful for assessing disability and are used to assess the effectiveness of pulmonary rehabilitation. Both the paced shuttle walk tests[152,153] and the unpaced 6-minute walk test can be used[154]. Laboratory testing using cycle or treadmill ergometry can identify co-existing or alternative conditions, e.g., cardiac diagnoses. Monitoring of physical activity may be more relevant regarding prognosis than evaluating exercise capacity[155]. This can be done using accelerometers or multisensor instruments.

Composite Scores. Several variables including FEV_1, exercise tolerance assessed by walking distance or peak oxygen consumption, weight loss, and reduction in arterial oxygen tension identify patients at increased risk for mortality. A relatively simple approach to identifying disease severity using a combination of most of the above variables has been proposed. The BODE method gives a composite score (Body mass index, Obstruction, Dyspnea, and Exercise) that is a better predictor of subsequent survival than any component singly[156], and its properties as a measurement tool are under investigation. Simpler alternatives not including an exercise test have been suggested but all these approaches need validation across a wide range of disease severities and in different clinical settings to confirm that they are suitable for routine clinical use[157,158].

DIFFERENTIAL DIAGNOSIS

In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiological testing techniques, and it is assumed that asthma and COPD coexist in these patients. In these cases, current management will include use of anti-inflammatory drugs and other treatments need to be individualized. Other potential diagnoses are usually easier to distinguish from COPD (**Table 2.7**).

Table 2.7. COPD and its Differential Diagnoses	
Diagnosis	**Suggestive Features**
COPD	Onset in mid-life. Symptoms slowly progressive. History of tobacco smoking or exposure to other types of smoke.
Asthma	Onset early in life (often childhood). Symptoms vary widely from day to day. Symptoms worse at night/early morning. Allergy, rhinitis, and/or eczema also present. Family history of asthma.
Congestive Heart Failure	Chest X-ray shows dilated heart, pulmonary edema. Pulmonary function tests indicate volume restriction, not airflow limitation.
Bronchiectasis	Large volumes of purulent sputum. Commonly associated with bacterial infection. Chest X-ray/CT shows bronchial dilation, bronchial wall thickening.
Tuberculosis	Onset all ages. Chest X-ray shows lung infiltrate. Microbiological confirmation. High local prevalence of tuberculosis.
Obliterative Bronchiolitis	Onset at younger age, nonsmokers. May have history of rheumatoid arthritis or acute fume exposure. Seen after lung or bone marrow transplantation. CT on expiration shows hypodense areas.
Diffuse Panbronchiolitis	Predominantly seen in patients of Asian descent. Most patients are male and nonsmokers. Almost all have chronic sinusitis. Chest X-ray and HRCT show diffuse small centrilobular nodular opacities and hyperinflation.

These features tend to be characteristic of the respective diseases, but are not mandatory. For example, a person who has never smoked may develop COPD (especially in the developing world where other risk factors may be more important than cigarette smoking); asthma may develop in adult and even in elderly patients.

CHAPTER

3

THERAPEUTIC OPTIONS

CHAPTER 3: THERAPEUTIC OPTIONS

KEY POINTS:

- In patients who smoke, smoking cessation is very important. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates.
- Appropriate pharmacologic therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.
- To date, none of the existing medications for COPD has been shown conclusively to modify the long-term decline in lung function.
- Each pharmacological treatment regimen needs to be patient-specific, guided by severity of symptoms, risk of exacerbations, drug availability, and the patient's response.
- Influenza and pneumococcal vaccination should be offered to every COPD patient; they appear to be more effective in older patients and those with more severe disease or cardiac comorbidity.
- All patients who get short of breath when walking on their own pace on level ground should be offered rehabilitation; it can improve symptoms, quality of life, and physical and emotional participation in everyday activities.

SMOKING CESSATION

Smoking cessation is the intervention with the greatest capacity to influence the natural history of COPD. Evaluation of the smoking cessation component in a long-term, multicenter study indicates that if effective resources and time are dedicated to smoking cessation, 25% long-term quit rates can be achieved[159].

Pharmacotherapies for Smoking Cessation

Nicotine Replacement Products. Nicotine replacement therapy in any form (nicotine gum, inhaler, nasal spray, transdermal patch, sublingual tablet, or lozenge) reliably increases long-term smoking abstinence rates[160-162] and is significantly more effective than placebo. Patients need to be informed about the proper use of these products to optimize efficacy. Medical contraindications to nicotine replacement therapy include unstable coronary artery disease, untreated peptic ulcer disease, and recent myocardial infarction or stroke[163]. Continuous chewing of nicotine gum produces secretions that are swallowed rather than absorbed through the buccal mucosa, results in little absorption, and can cause nausea. Acidic beverages, particularly coffee, juices, and soft drinks, interfere with the absorption of nicotine.

Pharmacologic. Varenicline[164], bupropion[165] and nortriptyline have been shown to increase long-term quit rates[161,163,166], but should always be used as one element in a supportive intervention program rather than on their own. Although more studies need to be conducted with these medications, a randomized controlled trial with counseling and support showed quit rates at one year of 30% with sustained-release bupropion alone and 35% with sustained-release bupropion plus nicotine patch[165]. The effectiveness of the antihypertensive drug clonidine is limited by side effects[161].

Recommendations for treating tobacco use and dependence are summarized in **Table 3.1**.

Table 3.1. Treating Tobacco Use and Dependence: A Clinical Practice Guideline—Major Findings and Recommendations[160]

1.	Tobacco dependence is a chronic condition that warrants repeated treatment until long-term or permanent abstinence is achieved.
2.	Effective treatments for tobacco dependence exist and all tobacco users should be offered these treatments.
3.	Clinicians and health care delivery systems must institutionalize the consistent identification, documentation, and treatment of every tobacco user at every visit.
4.	Brief smoking cessation counseling is effective and every tobacco user should be offered such advice at every contact with health care providers.
5.	There is a strong dose-response relation between the intensity of tobacco dependence counseling and its effectiveness.
6.	Three types of counseling have been found to be especially effective: practical counseling, social support as part of treatment, and social support arranged outside of treatment.
7.	First-line pharmacotherapies for tobacco dependence—varenicline, bupropion SR, nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patch—are effective and at least one of these medications should be prescribed in the absence of contraindications.
8.	Tobacco dependence treatments are cost effective relative to other medical and disease prevention interventions.

A five-step program for intervention (**Table 3.2**) provides a strategic framework helpful to health care providers interested in helping their patients stop smoking[160,167-169]. Because tobacco dependence is a chronic disease[160], clinicians should recognize that relapse is common and reflects the chronic nature of dependence and addiction, not failure on the part of the clinician or the patient.

Counseling delivered by physicians and other health professionals significantly increases quit rates over self-initiated strategies[170] (**Evidence A**). Even a brief (3-minute) period of counseling to urge a smoker to quit results in smoking cessation rates of 5-10%[171]. There is a strong dose-response relationship between counseling intensity and cessation success[172,173]. Ways to intensify treatment include increasing the length of the treatment session, the number of treatment sessions, and the number of weeks over which the treatment is delivered. Sustained quit rates of 10.9% at 6 months have been achieved when clinician tutorials and feedback are linked to counseling sessions[174]. With more complex interventions quit rates can reach 20-30%[172]. In a multicenter controlled clinical trial, a combination of physician advice, group support, skills training, and nicotine replacement therapy achieved a quit rate of 35% at 1 year and a sustained quit rate of 22% at 5 years[159].

Table 3.2. Brief Strategies to Help the Patient Willing to Quit[160,167-169]

1. **ASK**: Systematically identify all tobacco users at every visit. *Implement an office-wide system that ensures that, for EVERY patient at EVERY clinic visit, tobacco-use status is queried and documented.*
2. **ADVISE**: Strongly urge all tobacco users to quit. *In a clear, strong, and personalized manner, urge every tobacco user to quit.*
3. **ASSESS**: Determine willingness to make a quit attempt. *Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days).*
4. **ASSIST**: Aid the patient in quitting. *Help the patient with a quit plan; provide practical counseling; provide intra-treatment social support; help the patient obtain extra-treatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials.*
5. **ARRANGE**: Schedule follow-up contact. *Schedule follow-up contact, either in person or via telephone.*

PHARMACOLOGIC THERAPY FOR STABLE COPD

Overview of the Medications

Pharmacologic therapy for COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. To date, none of the existing medications for COPD has been conclusively shown to modify the long-term decline in lung function when this is tested as a primary or secondary outcome in clinical trials[126,159,175,176]. *Post-hoc* evidence of such an effect with long-acting bronchodilators and/or inhaled corticosteroids[133,143] requires confirmation in specifically designed trials.

The classes of medications commonly used in treating COPD are shown in **Table 3.3**. The choice within each class depends on the availability and cost of medication and the patient's response. Each treatment regimen needs to be patient-specific as the relationship between severity of symptoms, airflow limitation, and severity of exacerbations will differ between patients.

When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique is essential[177]. The choice of inhaler device will depend on availability, cost, the prescribing physician, and the skills and ability of the patient. COPD patients may have problems with coordination and find it hard to use a metered-dose inhaler (MDI). It is essential to ensure that inhaler technique is correct and to re-check this at each visit.

Alternative breath-activated or spacer devices are available. In general, particle deposition from dry powder inhalers (DPIs) will tend to be more central with the fixed airflow limitation and lower inspiratory flow rates in COPD[178,179]. However, as has been shown in asthma, patients are also likely to find the use of some dry powder inhalers difficult. For the MDI, the addition of a large or small volume spacer often overcomes coordination problems, and improves lower airway deposition and clinical benefit. Many drugs are available as nebulizer solutions and, for patients who are severely overinflated and consequently may have very low inspiratory flow rates, there may be theoretical advantages of nebulizer use. However, there is little randomized trial evidence for their benefit over other devices, and use of nebulizers will often depend on local preference, availability and price. Benefit should be judged symptomatically, since changes in lung function may be small and within the limits of repeatability. Nebulized treatment should only be continued if the patient reports clear symptomatic benefit that cannot be achieved by simpler, cheaper, and more portable alternatives.

Bronchodilators

Medications that increase the FEV_1 or change other spirometric variables, usually by altering airway smooth muscle tone, are termed bronchodilators[180], since the improvements in expiratory flow reflect widening of the airways rather than changes in lung elastic recoil. Such medications improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise[181,182], and improve exercise performance. The extent of these changes, especially in severe and very severe patients, is not easily predictable from the improvement in FEV_1[183,184].

Dose-response relationships using FEV_1 as the outcome are relatively flat with all classes of bronchodilators[185-188.] Toxicity is also dose-related. Increasing the dose of either a $beta_2$-agonist or an anticholinergic by an order of magnitude, especially when given by a nebulizer, appears to provide subjective benefit in acute episodes[189] but is not necessarily helpful in stable disease[190].

Bronchodilator medications are given on either an as-needed basis or a regular basis to prevent or reduce symptoms[185-188] (**Evidence A**) (**Table 3.4**).

Table 3.3. Formulations and Typical Doses of COPD Medications*					
Drug	**Inhaler (mcg)**	**Solution for Nebulizer (mg/ml)**	**Oral**	**Vials for Injection (mg)**	**Duration of Action (hours)**
Beta$_2$-agonists					
Short-acting					
Fenoterol	100-200 (MDI)	1	0.05% (Syrup)		4-6
Levalbuterol	45-90 (MDI)	0.21, 0.42			6-8
Salbutamol (albuterol)	100, 200 (MDI & DPI)	5	5 mg (Pill), 0.024%(Syrup)	0.1, 0.5	4-6
Terbutaline	400, 500 (DPI)		2.5, 5 mg (Pill)		4-6
Long-acting					
Formoterol	4.5-12 (MDI & DPI)	0.01¶			12
Arformoterol		0.0075			12
Indacaterol	75-300 (DPI)				24
Salmeterol	25-50 (MDI & DPI)				12
Tulobuterol			2 mg (transdermal)		24
Anticholinergics					
Short-acting					
Ipratropium bromide	20, 40 (MDI)	0.25-0.5			6-8
Oxitropium bromide	100 (MDI)	1.5			7-9
Long-acting					
Aclidinium bromide	322 (DPI)				12
Glycopyrronium bromide	44 (DPI)				24
Tiotropium	18 (DPI), 5 (SMI)				24
Combination short-acting beta$_2$-agonists plus anticholinergic in one inhaler					
Fenoterol/Ipratropium	200/80 (MDI)	1.25/0.5			6-8
Salbutamol/Ipratropium	75/15 (MDI)	0.75/0.5			6-8
Methylxanthines					
Aminophylline			200-600 mg (Pill)	240	Variable, up to 24
Theophylline (SR)			100-600 mg (Pill)		Variable, up to 24
Inhaled corticosteroids					
Beclomethasone	50-400 (MDI & DPI)	0.2-0.4			
Budesonide	100, 200, 400 (DPI)	0.20. 0.25, 0.5			
Fluticasone	50-500 (MDI & DPI)				
Combination long-acting beta$_2$-agonists plus corticosteroids in one inhaler					
Formoterol/Budesonide	4.5/160 (MDI) 9/320 (DPI)				
Formoterol/mometasone	10/200, 10/400 (MDI)				
Salmeterol/Fluticasone	50/100, 250, 500 (DPI) 25/50, 125, 250 (MDI)				
Vilanterol/Fluticasone furoate	25/100 (DPI)				
Systemic corticosteroids					
Prednisone			5-60 mg (Pill)		
Methyl-prednisolone			4, 8, 16 mg (Pill)		
Phosphodiesterase-4 inhibitors					
Roflumilast			500 mcg (Pill)		24

MDI=metered dose inhaler; DPI=dry powder inhaler; SMI=soft mist inhaler
*Not all formulations are available in all countries; in some countries, other formulations may be available.
¶Formoterol nebulized solution is based on the unit dose vial containing 20 mcg in a volume of 2.0 ml

Beta$_2$-agonists. The principal action of beta$_2$-agonists is to relax airway smooth muscle by stimulating beta$_2$-adrenergic receptors, which increases cyclic AMP and produces functional antagonism to bronchoconstriction. The bronchodilator effects of short-acting beta$_2$-agonists usually wear off within 4 to 6 hours[191,192]. Regular and as-needed use of short-acting beta-agonists improve FEV_1 and symptoms (**Evidence B**)[193]. The use of high doses of short-acting beta$_2$-agonists on an as-needed basis in patients already treated with long-acting bronchodilators is not supported by evidence, may be limited by side effects, and cannot be recommended. For single-dose, as-needed use in COPD, there appears to be no advantage in using levalbuterol over conventional bronchodilators[194].

Table 3.4. Bronchodilators in Stable COPD
• Bronchodilator medications are central to symptom management in COPD. • Inhaled therapy is preferred. • The choice between beta$_2$-agonist, anticholinergic, theophylline, or combination therapy depends on availability and individual patient response in terms of symptom relief and side effects. • Bronchodilators are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms. • Long-acting inhaled bronchodilators are convenient and more effective at producing maintained symptom relief than short-acting bronchodilators. • Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.

Long-acting inhaled beta$_2$-agonists show duration of action of 12 or more hours. Formoterol and salmeterol significantly improve FEV_1 and lung volumes, dyspnea, health-related quality of life and exacerbation rate[195-200] **(Evidence A**), but have no effect on mortality and rate of decline of lung function. Salmeterol reduces the rate of hospitalization[195] (**Evidence B**). Indacaterol is a once daily beta$_2$-agonist with a duration of action of 24 hours[201,202]. The bronchodilator effect is significantly greater than that of formoterol and salmeterol, and similar to tiotropium (**Evidence A**). Indacaterol has significant effects on breathlessness, health status and exacerbation rate (**Evidence B**). Its safety profile is similar to placebo; in clinical trials a significant number of patients (24% vs 7%) experienced cough following the inhalation of indacaterol[513-516].

Adverse effects. Stimulation of beta$_2$-adrenergic receptors can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm disturbances in susceptible patients, although these seem to have remarkably few clinical implications. Exaggerated somatic tremor is troublesome in some older patients treated with higher doses of beta$_2$-agonists, whatever the route of administration, and this limits the dose that can be tolerated. Although hypokalemia can occur, especially when treatment is combined with thiazide diuretics[203], and oxygen consumption can be increased under resting conditions[204], these metabolic effects show tachyphylaxis unlike the bronchodilator actions. Mild falls in PaO_2 can occur after administration of both short-and long-acting beta$_2$-agonists[205,206] but the clinical significance of these changes is doubtful. Despite the concerns raised some years ago related to beta$_2$-agonists in the management of asthma, further detailed study has found no association between beta$_2$-agonist use and an accelerated loss of lung function or increased mortality in COPD.

Anticholinergics. The most important effect in COPD patients of anticholinergic medications, such as ipratropium, oxitropium and tiotropium bromide, appears to be blockage of acetylcholine's effect on muscarinic receptors. Current short-acting drugs block M2 and M3 receptors and modify transmission at the pre-ganglionic junction, although these effects appear less important in COPD[207]. The long-acting anticholinergic tiotropium has a pharmacokinetic selectivity for the M3 and M1 receptors[208]. The bronchodilating effect of short-acting inhaled anticholinergics lasts longer than that of short-acting beta$_2$-agonists, with some bronchodilator effect generally apparent up to 8 hours after administration[191]. Among long-acting anticholinergics, acclidinium has a duration of at least 12 hours[552] whereas tiotropium and glycopyrronium have a duration of action of more than 24 hours[209-211]. Tiotropium reduces exacerbations and related hospitalizations, improves symptoms and health status[212] (**Evidence A**), and improves the effectiveness of pulmonary rehabilitation[213] (**Evidence B**). In a large, long-term clinical trial on patients with COPD, there was no effect of tiotropium added to other standard therapies on the rate of lung function decline and no evidence of cardiovascular risk[214]. In another large trial, tiotropium was superior to salmeterol in reducing exacerbations although the difference was small[215,517]. The long-acting anticholinergics aclidinium and glycopyrronium seem to have similar action on lung function and breathlessness as tiotropium, whereas far less data are available for other outcomes[552, 558].

Adverse effects. Anticholinergic drugs are poorly absorbed which limits the troublesome systemic effects seen with atropine[216]. Extensive use of this class of inhaled agents in a wide range of doses and clinical settings has shown them to be very safe. The main side effect is dryness of the mouth. Twenty-one days of inhaled tiotropium, 18 mcg/day as a dry powder, does not retard mucus clearance from the lungs[144]. Although occasional prostatic symptoms have been reported, there are no data to prove a true causal relationship. Some patients using ipratropium report a bitter, metallic taste. An unexpected small increase in cardiovascular events in COPD patients regularly treated with ipratropium bromide has been reported and requires further investigation[217,218]. Tiotropium delivered via the Respimat® soft mist inhaler was associated with a significantly increased risk of mortality compared with placebo in a meta-analysis[519]; however, the findings of the TIOSPIR® trial showed that there was no difference in mortality or rates of exacerbation when comparing tiotropium in a dry-powder inhaler to the Respimat® inhaler[559]. Use of solutions with a face mask has been reported to precipitate acute glaucoma, probably by a direct effect of the solution on the eye.

Methylxanthines. Controversy remains about the exact effects of xanthine derivatives. They may act as nonselective phosphodiesterase inhibitors, but have also been reported to have a range of non-bronchodilator actions, the significance of which is disputed[220-224]. Data on duration of action for conventional, or even slow-release, xanthine preparations are lacking in COPD.

Theophylline, the most commonly used methylxanthine, is metabolized by cytochrome P450 mixed function oxidases. Clearance of the drug declines with age. Many other physiological variables and drugs modify theophylline metabolism. Changes in inspiratory muscle function have been reported in patients treated with theophylline[220], but whether this reflects changes in spirometry or a primary effect on the muscle is not clear. All studies that have shown efficacy of theophylline in COPD were performed with slow-release preparations.

Theophylline is less effective and less well tolerated than inhaled long-acting bronchodilators[225] and is not recommended if those drugs are available and affordable. However, there is evidence for a modest bronchodilator effect compared with placebo in stable COPD[226] (**Evidence A**). There is also some evidence of symptomatic benefit compared to placebo[227]. Addition of theophylline to salmeterol produced a greater inprovement in FEV_1 and breathlessness than salmeterol alone[228] (**Evidence B**). Low-dose theophylline reduces exacerbations but does not improve post-bronchodilator lung function[227] (**Evidence B**).

Adverse effects. Toxicity is dose-related, a particular problem with the xanthine derivatives because their therapeutic ratio is small and most of the benefit occurs only when near-toxic doses are given[221,223,229]. Methylxanthines are nonspecific inhibitors of all phosphodiesterase enzyme subsets, which explains their wide range of toxic effects. Problems include the development of atrial and ventricular arrhythmias (which can prove fatal) and grand mal convulsions (which can occur irrespective of prior epileptic history). Other side effects include headaches, insomnia, nausea, and heartburn, and these may occur within the therapeutic range of serum theophylline. These medications also have significant interactions with commonly used medications such as digitalis, coumadin, etc. Unlike the other bronchodilator classes, xanthine derivatives may involve a risk of overdose (either intentional or accidental).

Combination Bronchodilator Therapy. Combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation for equivalent or lesser side effects[230]. For example, a combination of a short-acting $beta_2$-agonist and an anticholinergic produces greater and more sustained improvements in FEV_1 than either drug alone and does not produce evidence of tachyphylaxis over 90 days of treatment[191,231,232]. The combination of a $beta_2$-agonist, an anticholinergic, and/or theophylline may produce additional improvements in lung function[191,224,228,231-235] and health status[191,236]. Short-term combination therapy using formoterol and tiotropium has been shown to have a bigger impact on FEV_1 than the single components[237,238] (**Evidence B**). Combinations of short-acting $beta_2$-agonists and anticholinergics are also superior compared to either medication alone in improving FEV_1 and symptoms[231] (**Evidence B**). Combinations of a long-acting $beta_2$-agonist and a long-acting anticholinergic have shown a significant increase in lung function whereas the impact on patient reported outcomes is still limited[560]. There is still too little evidence to determine if a combination of long-acting bronchodilators is more effective than a long-acting anticholinergic alone for preventing exacerbations[561].

Corticosteroids

Inhaled Corticosteroids. The dose-response relationships and long-term safety of inhaled corticosteroids in COPD are not known. Only moderate to high doses have been used in long-term clinical trials. The efficacy and side effects of inhaled corticosteroids in asthma are dependent on the dose and type of corticosteroid[239], but whether this is also the case in COPD is unclear. The effects of corticosteroids on pulmonary and systemic inflammation in patients with COPD are controversial, and their role in the management of stable COPD is limited to specific indications.

Regular treatment with inhaled corticosteroids improves symptoms, lung function, and quality of life, and reduces the frequency of exacerbations[144] in COPD patients with an FEV_1 < 60% predicted[195,240-244] (**Evidence A**). Withdrawal from treatment with inhaled corticosteroids may lead to exacerbations in some patients[245]. Regular treatment with inhaled corticosteroids does not modify the long-term decline of FEV_1 nor mortality in patients with COPD[126,175,176,195,246,247,520] (**Evidence A**).

Adverse effects. Inhaled corticosteroid use is associated with higher prevalence of oral candidiasis, hoarse voice, and skin bruising[126,175]. Treatment with inhaled corticosteroids is associated with an increased risk of pneumonia[195,246-248]. While long-term treatment with triamcinolone acetonide is associated with an increased risk of reduced bone density, the evidence with other inhaled corticosteroids is controversial. One long-term study showed no effect of budesonide on bone density and fracture rate[175,249], and treatment over a three-year period with 500 mcg bid fluticasone propionate alone or in combination with salmeterol was not associated with decreased bone mineral density in a population of COPD patients with high prevalence of osteoporosis[250].

Combination Inhaled Corticosteroid/Bronchodilator Therapy. An inhaled corticosteroid combined with a long-acting beta$_2$-agonist is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate (**Evidence B**) to very severe COPD[195,240,243,244,246,251-253,521,522] (**Evidence A**). A large prospective clinical trial failed to demonstrate a statistically significant effect of combination therapy on mortality[195], but a subsequent meta-analysis found that combination therapy may reduce mortality with a number needed to treat (NNT) of 36[254] (**Evidence B**). Combination therapy is associated with an increased risk of pneumonia[255], but no other significant side effect (**Evidence A**). The addition of a long-acting beta$_2$-agonist/inhaled corticosteroid combination to tiotropium improves lung function and quality of life[256,257] and may further reduce exacerbations (**Evidence B**) but more studies of triple therapy are needed[258].

Oral Corticosteroids. Oral corticosteroids have numerous side effects. An important side effect of long-term treatment of COPD with systemic corticosteroids is steroid myopathy[259-261], which contributes to muscle weakness, decreased functionality, and respiratory failure in subjects with very severe COPD. In view of the well-known toxicity of long-term treatment with oral corticosteroids, prospective studies on the long-term effects of these drugs in COPD are limited[262,263].

Phosphodiesterase-4 Inhibitors

The principal action of phosphodiesterase-4 inhibitors is to reduce inflammation by inhibiting of the breakdown of intracellular cyclic AMP[264,265]. It is a once daily oral medication with no direct bronchodilator activity, although it has been shown to improve FEV$_1$ in patients treated with salmeterol or tiotropium[264]. Roflumilast reduces moderate and severe exacerbations treated with corticosteroids by 15-20% in patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations[266] (**Evidence A**). The effects on lung function are also seen when roflumilast is added to long-acting bronchodilators[266] (**Evidence A**). There are no direct comparison or add-on studies of roflumilast and inhaled corticosteroids. Phosphodiesterase-4 inhibitors should always be used in combination with at least one long-acting bronchodilator.

<u>Adverse effects.</u> Phosphodiesterase-4 inhibitors have more adverse effects than inhaled medications for COPD[264-266]. The most frequent adverse effects are nausea, reduced appetite, abdominal pain, diarrhea, sleep disturbances, and headache. Adverse effects led to increased withdrawal in clinical trials from the group receiving roflumilast. Adverse effects seem to occur early during treatment, are reversible, and diminish over time with continued treatment. In controlled studies an average unexplained weight loss of 2 kg has been seen and weight monitoring during treatment is advised as well as avoiding treatment with roflumilast in underweight patients. Roflumilast should also be used with caution in patients with depression. Roflumilast and theophylline should not be given together.

Other Pharmacologic Treatments

Vaccines. Influenza vaccination can reduce serious illness (such as lower respiratory tract infections requiring hospitalization[267]) and death in COPD patients[268-270] (**Evidence A**). Vaccines containing killed or live, inactivated viruses are recommended[271] as they are more effective in elderly patients with COPD[272]. The strains are adjusted each year for appropriate effectiveness and should be given once each year[273]. Pneumococcal polysaccharide vaccine is recommended for COPD patients 65 years and older, and also in younger patients with significant comorbid conditions such as cardiac disease[274-276.] In addition, this vaccine has been shown to reduce the incidence of community-acquired pneumonia in COPD patients younger than age 65 with an FEV$_1$ < 40% predicted[277] (**Evidence B**).

Alpha-1 Antitrypsin Augmentation Therapy. Young patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for alpha-1 antitrypsin augmentation therapy (**Evidence C**). However, this therapy is very expensive, is not available in most countries, and is not recommended for patients with COPD that is unrelated to alpha-1 antitrypsin deficiency.

Antibiotics. In older studies prophylactic, continuous use of antibiotics was shown to have no effect on the frequency of exacerbations in COPD[278-280], and a study that examined the efficacy of chemoprophylaxis undertaken in winter months over a period of 5 years concluded that there was no benefit[281]. Although recent studies have shown some effects of antibiotics on exacerbation rate[282,283], the role of this treatment is unclear. A recent trial of daily azithromycin showed efficacy on exacerbation end-points; however, treatment is not recommended because of an unfavorable balance between benefits and side effects[284]. Thus, the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is currently not indicated[285,286] (**Evidence B**)

Mucolytic (mucokinetic, mucoregulator) and Antioxidant Agents (ambroxol, erdosteine, carbocysteine, iodinated glycerol). The regular use of mucolytics in COPD has been evaluated in a number of long-term studies with controversial results[287-289]. Although a few patients with viscous sputum may benefit from mucolytics[290,291], the overall benefits seem to be very small; the widespread use of these agents cannot be recommended at present (**Evidence D**). Drugs like N-acetylcysteine may have antioxidant effects, leading to speculation that these medications could have a role in the treatment of patients with recurrent exacerbations[292-295,562] (**Evidence B**). There is some evidence that in COPD patients not receiving inhaled corticosteroids, treatment with mucolytics such as carbocysteine and N-acetylcysteine may reduce exacerbations[296,297,562] (**Evidence B**) although a Cochrane review showed little or no effect on the overall quality of life[523].

Immunoregulators (immunostimulators, immunomodulators). Studies using an immunoregulator in COPD report a decrease in the severity and frequency of exacerbations[298,299]. However, additional studies to examine the long-term effects of this therapy are required; at present, its regular use cannot be recommended[300].

Antitussives. Cough, although sometimes a troublesome symptom in COPD, has a significant protective role[301]. The regular use of antitussives is not recommended in stable COPD (**Evidence D**).

Vasodilators. The belief that pulmonary hypertension in COPD is associated with a poorer prognosis has provoked many attempts to reduce right ventricular afterload, increase cardiac output, and improve oxygen delivery and tissue oxygenation. Many agents have been evaluated, including inhaled nitric oxide, but the results have been uniformly disappointing. In patients with COPD, in whom hypoxemia is caused primarily by ventilation-perfusion mismatching rather than by increased intrapulmonary shunt (as in noncardiogenic pulmonary edema), inhaled nitric oxide can worsen gas exchange because of altered hypoxic regulation of ventilation-perfusion balance[302,303]. Therefore, based on the available evidence, nitric oxide is contraindicated in stable COPD. Likewise, guidelines on the treatment of pulmonary hypertension do not recommend the use of endothelium-modulating agents for the treatment of pulmonary hypertension associated with COPD until data on their safety and efficacy in this condition are available[304].

Narcotics (morphine). Oral and parenteral opioids are effective for treating dyspnea in COPD patients with very severe disease. There is insufficient data to conclude whether nebulized opioids are effective[305]. However, some clinical studies suggest that morphine used to control dyspnea may have serious adverse effects and its benefits may be limited to a few sensitive subjects[306-310].

Others. Nedocromil and leukotriene modifiers have not been adequately tested in COPD patients and cannot be recommended. There was no evidence of benefit—and some some evidence of harm (malignancy and pneumonia)—from an anti-TNF-alpha antibody (infliximab) tested in moderate to severe COPD[311]. There is no evidence for the effectiveness of herbal medicines in treating COPD[312] and other alternative healing methods (e.g., acupuncture and homeopathy) have not been adequately tested.

NON-PHARMACOLOGIC THERAPIES

Rehabilitation

The principal goals of pulmonary rehabilitation are to reduce symptoms, improve quality of life, and increase physical and emotional participation in everyday activities[313,314]. To accomplish these goals, pulmonary rehabilitation covers a range of non-pulmonary problems that may not be adequately addressed by medical therapy for COPD, including exercise de-conditioning, relative social isolation, altered mood states (especially depression), muscle wasting, and weight loss. Pulmonary rehabilitation has been carefully evaluated in a large number of clinical trials and shown to increase peak workload, peak oxygen consumption, and endurance time[315]. Benefits have been reported from rehabilitation programs conducted in inpatient, outpatient, and home settings[315,316]; considerations of cost and availability most often determine the choice of setting. The various benefits of pulmonary rehabilitation are summarized in **Table 3.5**[313,314,317-320]. However the increased exercise capacity may not necessarily translate into increased daily physical activity[563].

Table 3.5. Benefits of Pulmonary Rehabilitation in COPD
• Improves exercise capacity (**Evidence A**).
• Reduces the perceived intensity of breathlessness (**Evidence A**).
• Improves health-related quality of life (**Evidence A**).
• Reduces the number of hospitalizations and days in the hospital (**Evidence A**).
• Reduces anxiety and depression associated with COPD (**Evidence A**).
• Strength and endurance training of the upper limbs improves arm function (**Evidence B**).
• Benefits extend well beyond the immediate period of training (**Evidence B**).
• Improves survival (**Evidence B**).
• Respiratory muscle training can be beneficial, especially when combined with general exercise training (**Evidence C**).
• Improves recovery after hospitalization for an exacerbation (**Evidence A**)[524].
• Enhances the effect of long-acting bronchodilators (**Evidence B**).

The minimum length of an effective rehabilitation program is 6 weeks; the longer the program continues, the more effective the results[321-323]. However, as yet, no effective program has been developed to maintain the effects over time[324]. Many physicians advise patients unable to participate in a structured program to exercise on their own (e.g., walking 20 minutes daily). The benefits of this general advice have not been tested, but because observational studies have indicated significant benefits of physical activity[325,326], and because physical activity is good for so many other reasons, it is highly reasonable to offer such advice to patients if a formal program is not available.

Components of Pulmonary Rehabilitation Programs

The components of pulmonary rehabilitation vary widely but a comprehensive programs includes exercise training, smoking cessation, nutrition counseling, and education.

Exercise training. Exercise tolerance can be assessed by either bicycle ergometry or treadmill exercise with the measurement of a number of physiological variables, including maximum oxygen consumption, maximum heart rate, and maximum work performed. A less complex approach is to use a self-paced, timed walking test (e.g., 6-minute walking distance). These tests require at least one practice session before data can be interpreted. Shuttle walking tests offer a compromise: they provide more complete information than an entirely self-paced test, but are simpler to perform than a treadmill test[153].

Exercise training ranges in frequency from daily to weekly, in duration from 10 minutes to 45 minutes per session, and in intensity from 50% peak oxygen consumption (VO_2 max) to maximum tolerated[253]. The optimum length for an exercise program has not been investigated in randomized controlled trials but most studies involving fewer than 28 exercise sessions show inferior results compared to those with longer treatment periods[327]. In practice, the length depends on the resources available and usually ranges from 4 to 10 weeks, with longer programs resulting in larger effects than shorter programs[318].

In many programs, especially those using simple corridor exercise training, the patient is encouraged to walk to a symptom-limited maximum, rest, and then continue walking until 20 minutes of exercise have been completed. Where possible, endurance exercise training to 60-80% of the symptom-limited maximum is preferred. Endurance training can be accomplished through continuous or interval exercise programs. The latter involve the patient doing the same total work but divided into briefer periods of high-intensity exercise, which is useful when performance is limited by other comorbidities[328,329]. Use of a simple wheeled walking aid seems to improve walking distance and reduces breathlessness in severely disabled COPD patients[330-332]. Other approaches to improving outcomes such as use of oxygen during exercise[333], exercising while breathing heliox gas mixtures[334], or unloading the ventilator muscles while exercising remain experimental at present.

Some programs also include upper limb exercises, usually involving an upper limb ergometer or resistive training with weights. There are no randomized clinical trial data to support the routine inclusion of these exercises, but they may be helpful in patients with comorbidities that restrict other forms of exercise and those with evidence of respiratory muscle weakness[335]. In contrast, inspiratory muscle training appears to provide additional benefits when included in a comprehensive pulmonary rehabilitation program[336-338]. The addition of upper limb exercises or other strength training to aerobic training is effective in improving strength, but does not improve quality of life or exercise tolerance[339].

The following points summarize current knowledge of considerations important in choosing patients for pulmonary rehabilitation:

Functional status: Benefits have been seen in patients with a wide range of disability, although those who are chair-bound appear less likely to respond even to home visiting programs[340] (**Evidence B**).

Severity of dyspnea: Stratification by breathlessness intensity using the mMRC questionnaire may be helpful in selecting patients most likely to benefit from rehabilitation. Those with mMRC grade 4 dyspnea may not benefit[340] (**Evidence B**).

Motivation: Selecting highly motivated participants is especially important in the case of outpatient programs[341].

Smoking status: There is no evidence that smokers will benefit less than nonsmokers, although some suggest that continuing smokers are less likely to complete pulmonary rehabilitation programs than nonsmokers[341] (**Evidence B**).

Education. Most pulmonary rehabilitation programs include an educational component. The topics that seem most appropriate for an education program include: smoking cessation; basic information about COPD; general approach to therapy and specific aspects of medical treatment; self-management skills; strategies to help minimize dyspnea; advice about when to seek help; decision-making during exacerbations; and advance directives and end-of-life issues.

The intensity and content of these educational messages should vary depending on the severity of the patient's disease, although the specific contributions of education to the improvements seen after pulmonary rehabilitation remain unclear. Studies indicate that patient education alone does not improve exercise performance or lung function[342-345], but it can play a role in improving skills, ability to cope with illness, and health status[346]. These outcomes are not traditionally measured in clinical trials,but they may be most important in COPD where even pharmacologic interventions generally confer only a small benefit in terms of lung function.

Patients with severe COPD often express the desire to discuss end-of-life care with clinicians, but these conversations rarely occur in clinical practice. Simple, structured approaches to facilitate these conversations may help to improve the occurrence and quality of communication from the patients' perspective[525]. In particular, patients with a chronic life-limiting illness like COPD should be informed that, should they become critically ill, they or their family members may be in a position where they would need to decide whether a) a course of intensive care is likely to achieve their personal goals of care, and b) they are willing to accept the burdens of such treatment. Communication about end-of-life care and advance care planning gives patients the opportunity to make informed decisions about the kind of care they want and ensure that their family and clinicians understand their values, goals, and perspectives[526]. Clinicians should develop and implement methods to help patients and their families to make informed choices that are consistent with patients' values. Such methods have the potential to improve the quality of care and simultaneously may contribute to efforts to reduce health care costs by ensuring patients receive care consistent with their goals and values[527,528].

Assessment and Follow-up. Baseline and outcome assessments of each participant in a pulmonary rehabilitation program should be made to quantify individual gains and target areas for improvement. Assessments should include:

- Detailed history and physical examination
- Measurement of post-bronchodilator spirometry
- Assessment of exercise capacity
- Measurement of health status and impact of breathlessness (e.g., CAT and mMRC scales)
- Assessment of inspiratory and expiratory muscle strength and lower limb strength (e.g., quadriceps) in patients who suffer from muscle wasting

The first two assessments are important for establishing entry suitability and baseline status but are not used in outcome assessment. The last three assessments are baseline and outcome measures. Several detailed questionnaires for assessing health status are available, including some that are specifically designed for patients with respiratory disease (e.g., *Chronic Respiratory Disease Questionnaire*[236], *St. George Respiratory Questionnaire*[347], *Chronic Obstructive Pulmonary Disease Assessment Test*[124]), and there is increasing evidence that these questionnaires may be useful in a clinical setting. Health status can also be assessed by generic questionnaires, such as the *Medical Outcomes Study Short Form (SF36)*[348], to enable comparison of quality of life in different diseases. The *Hospital Anxiety and Depression Scale (HADS)*[349] and the *Primary Care Evaluation of Mental Disorders (PRIME-MD) Patient Questionnaire*[350] have been used to improve identification and treatment of anxious and depressed patients.

Nutritional support. Low-to-moderate quality evidence suggests that nutritional support promotes significant gain in weight and fat-free mass among patients with COPD, especially if malnourished. In addition, significantly greater changes from baseline have been observed in supplemented patients for six-minute walk test, respiratory muscle strength and (only in malnourished patients) overall HRQoL as measured by SGRQ. Positive effects have been observed when nutritional supplementation is proposed alone or as an adjunct to exercise training. The optimal amount and duration of supplementation are not clearly established[564].

OTHER TREATMENTS

Oxygen Therapy

The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival in patients with severe resting hypoxemia[359] (**Evidence B**). Long-term oxygen therapy is indicated for patients who have:

- PaO_2 at or below 7.3 kPa (55 mmHg) or SaO_2 at or below 88%, with or without hypercapnia confirmed twice over a three week period (**Evidence B**); or
- PaO_2 between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO_2 of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%) (**Evidence D**).

A decision about the use of long-term oxygen should be based on the resting PaO_2 or saturation values repeated twice over three weeks in the stable patient. Current data do not support the use of ambulatory oxygen in patient populations that do not meet the above criteria[360].

Although air travel is safe for most patients with chronic respiratory failure who are on long-term oxygen therapy[529], patients should ideally be able to maintain an in-flight PaO_2 of at least 6.7 kPa (50 mmHg). Studies indicate that this can be achieved in those with moderate to severe hypoxemia at sea level by supplementary oxygen at 3 L/min by nasal cannulae or 31% by Venturi facemask[361]. Those with a resting PaO_2 at sea level > 9.3 kPa (70 mmHg) are likely to be safe to fly without supplementary oxygen[362,363], although it is important to emphasize that a resting PaO_2 > 9.3 kPa (70 mmHg) at sea level does not exclude the development of severe hypoxemia when travelling by air (**Evidence C**). Careful consideration should be given to any comorbidity that may impair oxygen delivery to tissues (e.g., cardiac impairment, anemia). Also, walking along the aisle may profoundly aggravate hypoxemia[364].

Ventilatory Support

Non-invasive ventilation (NIV) is increasingly used in patients with stable very severe COPD. The combination of NIV with long-term oxygen therapy may be of some use in a selected subset of patients, particularly in those with pronounced daytime hypercapnia[365]. It may improve survival but does not improve quality of life[365]. However, in patients with both COPD and obstructive sleep apnea there are clear benefits from continuous positive airway pressure (CPAP) in both survival and risk of hospital admission[366].

Surgical Treatments

Lung Volume Reduction Surgery (LVRS). LVRS is a surgical procedure in which parts of the lung are resected to reduce hyperinflation[367], making respiratory muscles more effective pressure generators by improving their mechanical efficiency (as measured by length/tension relationship, curvature of the diaphragm, and area of apposition)[368,369]. In addition, LVRS increases the elastic recoil pressure of the lung and thus improves expiratory flow rates and reduces exacerbations[370]. The advantage of surgery over medical therapy is more significant among patients with predominantly upper-lobe emphysema and low exercise capacity prior to treatment. A prospective economic analysis indicated that LVRS is costly relative to health-care programs not including surgery[371]. In contrast to medical treatment, LVRS has been demonstrated to result in improved survival (54% vs. 39.7%) in severe emphysema patients with upper-lobe emphysema and low post-rehabilitation exercise capacity[372] (**Evidence A**). In similar patients with high post-pulmonary rehabilitation exercise capacity no difference in survival was noted after LVRS, although health-related quality of life and exercise capacity improved. LVRS has been demonstrated to result in higher mortality than medical management in severe emphysema patients with an FEV_1 ≤ 20% predicted and either homogeneous emphysema on high resolution computed tomography or a DL_{CO} ≤ 20% predicted[373].

Bronchoscopic Lung Volume Reduction (BLVR). In a post-hoc analysis, BLVR in COPD patients with severe airflow limitation (FEV_1 15-45% predicted), heterogeneous emphysema on CT scan, and hyperinflation (TLC > 100% and RV > 150% predicted) has been demonstrated to result in modest improvements in lung function, exercise tolerance, and symptoms at the cost of more frequent exacerbations of COPD, pneumonia, and hemoptysis after implantation[374]. Additional data are required to define the optimal technique and patient population.

Lung Transplantation. In appropriately selected patients with very severe COPD, lung transplantation has been shown to improve quality of life and functional capacity[375,376]. The common complications seen in COPD patients after lung transplantation, apart from post-operative mortality, are acute rejection, bronchiolitis obliterans, opportunistic infections such as CMV, fungal (*Candida, Aspergillus, Cryptococcus, Pneumocystis*) or bacterial (*Pseudomonas, Staphylococcus species*) infections, and lymphoproliferative disease[377]. Lung transplantation is limited by the shortage of donor organs and costs. Criteria for referral for lung transplantation include COPD with a BODE index exceeding 5. Recommended criteria for listing include a BODE index of 7-10 and at least one of the following: history of exacerbation associated with acute hypercapnia [$PaCO_2$ > 6.7 kPa (50 mmHg)]; pulmonary hypertension, cor pulmonale, or both despite oxygen therapy; and FEV_1 < 20% predicted with either DL_{CO} < 20% predicted or homogenous distribution of emphysema[378] (**Evidence C**).

Bullectomy. Bullectomy is an older surgical procedure for bullous emphysema. Removal of a large bulla that does not contribute to gas exchange decompresses the adjacent lung parenchyma. Pulmonary hypertension, hypercapnia, and severe emphysema are not absolute contraindications for bullectomy.

Palliative Care, End-of-life Care, and Hospice Care.

The disease trajectory in COPD is usually marked by a gradual decline in health status and increasing symptoms, punctuated by acute exacerbations that are associated with an increased risk of dying[530]. Although mortality following hospitalization for an acute exacerbation of COPD is falling[531], it still varies between 23%[532] and 80%[533]. Progressive respiratory failure, cardiovascular diseases, malignancies and other diseases are the primary cause of death in patients with COPD hospitalized for an exacerbation[533]. For all these reasons, palliative care, end-of-life care, and hospice care are important components of the care of patients with advanced COPD.

Palliative care is the broadest term and incorporates (but is not limited to) both end-of-life care (care for those who are actively dying) as well as hospice care (a model for delivery of end-of-life care for patients who are terminally ill and predicted to have less than 6 months to live). The goal of palliative care is to prevent and relieve suffering, and to support the best possible quality of life for patients and their families, regardless of the stage of disease or the need for other therapies[534]. Therefore, palliative care is an important component in the management of all patients with advanced COPD and should begin at the time of the diagnosis of a chronic life-limiting illness such as COPD; yet patients with COPD are less likely to receive such services than patients with lung cancer[535,536]. Palliative care expands traditional disease-model medical treatment to increase the focus on the goals of enhancing quality of life, optimizing function, helping with decision making about end-of-life care, providing emotional and spiritual support to patients and their families[534]. Increasingly, palliative care teams are available for consultation for hospitalized patients and such teams are rapidly increasing in numbers and capacity[537]. Availability for outpatient palliative care consultation is less common, but has been shown to improve quality of life, reduce symptoms and even prolong survival for some patients, such as those with advanced lung cancer[536]. Clinicians caring for patients with COPD should help identify patients who could benefit from palliative care services and identify available palliative care resources within their community for these patients.

For patients with the most advanced and terminal illness, hospice services may provide additional benefit. Hospice services often focus on patients with severe disability or symptom burden and may provide these services within the patient's home or in hospice beds in dedicated hospice units or other institutions such as hospitals or nursing homes. The National Hospice and Palliative Care Organization (http://www.nhpco.org) provides guidance for for selecting patients with non-cancer diseases like COPD for access to hospice services (for example, disabling dyspnea at rest that is poorly responsive to bronchodilators and progression of advanced disease demonstrated by increasing hospitalizations or emergency department visits)[535,536]. These guidelines discuss the difficulties in accurately predicting the prognosis of patients with advanced COPD, but recognize the appropriateness of providing hospice services for some of these patients[534].

CHAPTER

4

MANAGEMENT OF STABLE COPD

CHAPTER 4: MANAGEMENT OF STABLE COPD

KEY POINTS:

- Identification and reduction of exposure to risk factors are important steps in the prevention and treatment of COPD. All individuals who smoke should be encouraged to quit.
- The level of FEV_1 is an inadequate descriptor of the impact of the disease on patients and for this reason individualized assessment of symptoms and future risk of exacerbation should also be incorporated into the management strategy for stable COPD.
- Pharmacologic therapy is used to reduce symptoms, reduce frequency and severity of exacerbations, and improve health status and exercise tolerance. Existing medications for COPD have not been conclusively shown to modify the long-term decline in lung function that is the hallmark of this disease.
- For both $beta_2$-agonists and anticholinergics, long-acting formulations are preferred over short-acting formulations. Based on efficacy and side effects, inhaled bronchodilators are preferred over oral bronchodilators.
- Long-term treatment with inhaled corticosteroids added to long-acting bronchodilators is recommended for patients at high risk of exacerbations.
- Long-term monotherapy with oral or inhaled corticosteroids is not recommended in COPD.
- The phosphodiesterase-4 inhibitor roflumilast may be useful to reduce exacerbations for patients with FEV_1 < 50% predicted, chronic bronchitis, and frequent exacerbations.
- Influenza vaccines can reduce the risk of serious illness (such as hospitalization due to lower respiratory tract infections) and death in COPD patients.
- Currently, the use of antibiotics is not indicated in COPD, other than for treating infectious exacerbations of COPD and other bacterial infections.
- All COPD patients with breathlessness when walking at their own pace on level ground appear to benefit from rehabilitation and maintenance of physical activity, improving their exercise tolerance and quality of life, and reducing symptoms of dyspnea and fatigue.

INTRODUCTION

Once COPD has been diagnosed, effective management should be based on an individualized assessment of disease in order to reduce both current symptoms and future risks (**Table 4.1**). These goals should be reached with minimal side effects from treatment, a particular challenge in COPD patients because they commonly have comorbidities that also need to be carefully identified and treated.

Table 4.1. Goals for Treatment of Stable COPD

• Relieve symptoms • Improve exercise tolerance • Improve health status	→ REDUCE SYMPTOMS
and	
• Prevent disease progression • Prevent and treat exacerbations • Reduce mortality	→ REDUCE RISK

It is crucial for patients with COPD to understand the nature of their disease, the risk factors for its progression, and their role and that of their health care workers in achieving optimal management and health outcomes. The type of health care workers seen, and the frequency of visits, will depend on the health care system. Ongoing monitoring should ensure that the goals of treatment are being met and should include continuous evaluation of exposure to risk factors and monitoring of disease progression, the effect of treatment and possible adverse effects, exacerbation history, and comorbidities. In addition, patients should receive general advice on healthy living, including diet and the fact that physical exercise is safe and encouraged for people with COPD.

Identification and reduction of exposure to risk factors are important in the treatment and prevention of COPD. Since cigarette smoking is the most commonly encountered and easily identifiable risk factor, smoking cessation should be encouraged for all individuals who smoke. Reduction of total personal exposure to occupational dusts, fumes, and gases and to indoor and outdoor air pollutants may be more difficult but should be attempted.

IDENTIFY AND REDUCE EXPOSURE TO RISK FACTORS

Tobacco Smoke

Smoking cessation is the key intervention for all COPD patients who continue to smoke (**Evidence A**). Health care providers are important to the delivery of smoking cessation messages and interventions and should encourage all patients who smoke to quit, even when patients visit a health care provider for reasons unrelated to COPD or breathing problems.

Occupational Exposures

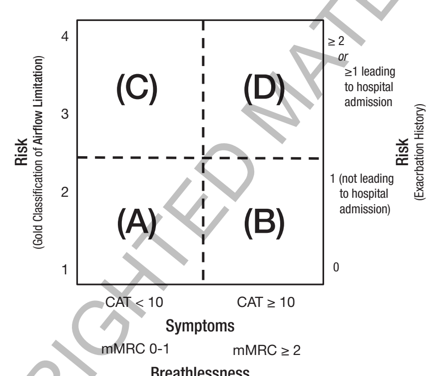
Although studies as yet have not been done to demonstrate whether interventions to reduce occupational exposures also reduce the burden of COPD, it seems common sense to advise patients to avoid continued exposures to potential aggravants, if possible (**Evidence D**).

Indoor and Outdoor Air Pollution

Reducing the risk from indoor and outdoor air pollution is feasible and requires a combination of public policy, local and national resources, cultural changes, and protective steps taken by individual patients. Reduction of exposure to smoke from biomass fuel, particularly among women and children, is a crucial goal to reduce the prevalence of COPD worldwide. Efficient ventilation, non-polluting cooking stoves, use of flues, and similar interventions are feasible and should be recommended[379,380] (**Evidence B**).

Table 4.2. Model of Symptom/Risk of Evaluation of COPD

When assessing risk, choose the highest risk according to GOLD grande or exacerbation history. (One or more hospitalizations for COPD exacerbations should be considered high risk.)



Patient Category	Characteristics	Spirometric Classification	Exacerbations per year	CAT	mMRC
A	Low Risk, Less Symptoms	GOLD 1-2	≤1	< 10	0-1
B	Low Risk, More Symptoms	GOLD 1-2	≤1	≥ 10	≥ 2
C	High Risk, Less Symptoms	GOLD 3-4	≥ 2	< 10	0-1
D	High Risk, More Symptoms	GOLD 3-4	≥ 2	≥ 10	≥ 2

TREATMENT OF STABLE COPD

In previous versions of the GOLD report, COPD treatment recommendations were based on spirometry only. This is in keeping with the fact that most of the clinical trial evidence about treatment efficacy in COPD is oriented around baseline FEV_1. However, FEV_1 alone is a poor descriptor of disease status and for this reason the treatment strategy for stable COPD should also consider an individual patient's symptoms and future risk of exacerbations. This individualized assessment is summarized in **Table 4.2**.

Moving from Clinical Trials to Recommendations for Routine Practice – Considerations

The guidance for clinical practice presented below is based on evidence from clinical trials, as detailed in the discussion of Evidence Levels at the beginning of this document. However, it is important to recognize that all clinical trials recruit restricted groups of patients; this limits their generalizability. In COPD the key inclusion criteria are: baseline FEV_1, acute bronchodilator reversibility, smoking history, symptoms and a prior history of exacerbations. A few general considerations related to these inclusion criteria are discussed below.

Baseline FEV_1. The evidence for pharmacological treatment of COPD is mostly based on the severity of airflow limitation (FEV_1 % predicted), and GOLD spirometry classification has often been used as an entry criterion for clinical trials. There is almost no evidence on efficacy of COPD treatments in patients with FEV_1 > 70% predicted (GOLD 1), and no evidence at all concerning anti-inflammatory treatment in patients with FEV_1 > 60% predicted. Many studies of combination medications (inhaled corticosteroids plus long-acting $beta_2$-agonists) have been limited to GOLD 3-4 (Severe-Very Severe airflow limitation) patients. As no trials have been carried out purely in GOLD 2 patients, evidence of the efficacy of combination treatment in this group has to be drawn from studies that included such patients as a subset of participants. Large studies such as TORCH[195] and UPLIFT[214] each contained over 2,000 GOLD 2 patients, albeit in the lower stratum of GOLD 2 (FEV_1 < 60% predicted). In general, it is important to draw a distinction between absence of evidence that a treatment works and presence of evidence that a treatment does not work.

Acute Bronchodilator Reversibility. Many COPD trials have used low reversibility of airflow limitation as an entry criterion. Acute reversibility is not a reliable measurement[381] and, in general, acute reversibility in response to bronchodilator is a poor predictor of a treatment's benefit for FEV_1 after one year[382]. Thus, this common clinical trial entry criterion has limited impact on the reliability of therapeutic recommendations.

Symptoms. Almost all studies have included patients with respiratory symptoms; there are no data on asymptomatic patients. No studies have reported results based upon stratified symptom levels.

Exacerbation Prevention. Studies in which exacerbations are a major outcome often "enrich" the patient population by requiring a history of frequent exacerbations in the preceding year, as it is often easier to demonstrate an effect of treatment preventing exacerbations if the exacerbations actually occur. However, large trials that have not used this entry criterion have also shown reductions in exacerbations, even in patients with less severe airflow limitation[195,214]. The patient's own history of exacerbations appears to be the most powerful predictor of future exacerbations[132], so the GOLD panel assumed that it is safe to extrapolate evidence of efficacy from clinical trials to appropriate patients in routine practice, regardless of the trial's entry criteria concerning previous exacerbation history.

Sub-Group Analysis. Results of clinical trials potentially apply to every member of the intention-to-treat population, whether they lie in the center of the distribution of severity or at the extremes. Sub-group analysis, whether pre-specified or not, must be used with caution. For example, if a treatment has no effect in the intention-to-treat population, but appears to have an effect that is confined to one sub-group, there is a strong likelihood that one of the other groups would be worse on the treatment. In contrast, subgroup analysis is useful if it shows that a treatment effect is consistent in size and direction across the range of patients recruited to the study. In summary, sub-group analysis does not provide robust evidence that a treatment works in a specific subgroup, but it can provide confidence that the results from the intention-to-treat population apply to patients who met the study entry criteria. Subgroup analysis can also generate hypotheses to be tested in subsequent trials.

NON-PHARMACOLOGIC TREATMENT

Non-pharmacologic management of COPD according to the individualized assessment of symptoms and exacerbation risk is shown in **Table 4.3**.

Smoking Cessation

Smoking cessation should be considered the most important intervention for all COPD patients who smoke regardless of the level of disease severity.

Physical Activity

Physical activity is recommended for all patients with COPD. There is very little COPD-specific evidence to support recommendations for physical activity other than studies of pulmonary rehabilitation (the physical exercise component is believed to provide the most benefit). However, given the overall population benefits of physical exercise and its role in primary and secondary prevention of cardiovascular disease, it seems intuitively correct to recommend daily physical activity.

Rehabilitation

Although more information is needed on criteria for patient selection for pulmonary rehabilitation programs, all COPD patients appear to benefit from rehabilitation and maintenance of physical activity, improving their exercise tolerance and experiencing decreased dyspnea and fatigue[383] (**Evidence A**). Several studies have documented an effect of pulmonary rehabilitation in patients with breathlessness, usually mMRC > 1, and following acute exacerbations. Data suggest that these benefits can be sustained even after a single pulmonary rehabilitation program[341,384,385]. Benefit does wane after a rehabilitation program ends, but if exercise training is maintained at home the patient's health status remains above pre-rehabilitation levels (**Evidence B**).

Vaccination

Decisions about vaccination in COPD patients depend on local policies, availability, and affordability.

Table 4.3. Non-Pharmacologic Management of COPD

Patient Group	***Essential***	***Recommended***	***Depending on Local Guidelines***
A	Smoking cessation (can include pharmacologic treatment)	Physical activity	Flu vaccination Pneumococcal vaccination
B-D	Smoking cessation (can include pharmacologic treatment) Pulmonary rehabilitation	Physical activity	Flu vaccination Pneumococcal vaccination

PHARMACOLOGIC TREATMENT

Pharmacologic therapy in COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. Existing medications for COPD have not been conclusively shown to modify the long-term decline in lung function that is the hallmark of this disease[126,159,175,176].

The classes of medications commonly used in treating COPD are shown in **Table 3.3** and a detailed description of the effects of these medications is given in Chapter 3. The choice within each class depends on the availability of medication and the patient's response. A proposed model for initial pharmacological management of COPD according to the individualized assessment of symptoms and exacerbation risk is shown in **Table 4.4**.

Group A patients have few symptoms and a low risk of exacerbations. Specific evidence for the effectiveness of pharmacologic treatments is not available for patients with FEV_1 > 80% predicted (GOLD 1). However, for all Group A patients, a short-acting bronchodilator used as needed is recommended as first choice based on its effect on lung function and breathlessness[565]. An alternative choice is a combination of short-acting bronchodilators or the introduction of a long-acting bronchodilator. The evidence for this step-up is weak; few studies of the combination exist[191,386], and most trials of therapy with long-acting bronchodilators have been performed in patients with more severe airflow limitation[212,387].

Group B patients have more significant symptoms but still a low risk of exacerbations. Long-acting bronchodilators are superior to short-acting bronchodilators (taken as needed, or prn) and are therefore recommended[212,387]. There is no evidence to recommend one class of long-acting bronchodilators over another for initial treatment. In the individual patient, the choice should depend on the patient's perception of symptom relief. For patients with severe breathlessness, the alternative choice is a combination of long-acting bronchodilators[237,238]. Only short-term studies of this treatment option have been reported and patients on a combination of long-acting bronchodilators should be carefully followed and their treatment effect evaluated. Other possible treatments include short-acting bronchodilators and theophylline, the latter of which can be used if inhaled bronchodilators are unavailable or unaffordable.

Group C patients have few symptoms but a high risk of exacerbations. As first choice a fixed combination of inhaled corticosteroid/long-acting beta$_2$-agonist or a long-acting anticholinergic is recommended[195,212,214,240,244,251,388]. Unfortunately, there is only one study directly comparing these treatments, which makes differentiation difficult[389]. As an alternative choice a combination of two long-acting bronchodilators or the combination of inhaled corticosteroid/long-acting anticholinergic can be used. Both long-acting anticholinergic and long-acting beta$_2$-agonist reduce the risk of exacerbations[212,387], and although good long-term studies are lacking, this principle of combination treatment seems sound (although in many countries expensive). The recommendation for a combination of inhaled corticosteroid/long-acting anticholinergic is not evidence-based, but this lack of evidence seems to be the result of lack of interest from the pharmaceutical industry rather than doubts about the rationale. A phosphodiesterase-4 inhibitor used in combination with at least one long-acting bronchodilator could be considered if the patient has chronic bronchitis[264,266]. Other possible treatments include short-acting bronchodilators and theophylline if long-acting inhaled bronchodilators are unavailable or unaffordable.

Group D patients have many symptoms and a high risk of exacerbations. The first choice of therapy is inhaled corticosteroid plus long-acting beta$_2$-agonist or long-acting anticholinergic, although there are conflicting findings concerning this treatment[257]; support for it mainly comes from short-term studies[257,538,539] (**Evidence B**). As second choice a combination of all three classes of drugs (inhaled corticosteroids/long-acting beta$_2$-agonist/long-acting anticholinergic) is recommended[256]. It is also possible to add a phosphodiesterase-4 inhibitor to the treatment chosen as first choice, provided the patient has chronic bronchitis[266]. A phosphodiesterase-4 inhibitor is effective when added to a long-acting bronchodilator[264], whereas evidence of its benefit when added to inhaled corticosteroid comes from less valid secondary analyses. Other possible treatments include short-acting bronchodilators, and theophylline or carbocysteine[296] can be used if long-acting inhaled bronchodilators are unavailable or unaffordable.

Bronchodilators – Recommendations

- For both beta$_2$-agonists and anticholinergics, long-acting formulations are preferred over short-acting formulations (**Evidence A**).
- The combined use of short- or long-acting beta$_2$-agonists and anticholinergics may be considered if symptoms are not improved with single agents (**Evidence B**).
- Based on efficacy and side effects inhaled bronchodilators are preferred over oral bronchodilators (**Evidence A**).
- Based on evidence of relatively low efficacy and more side effects, treatment with theophylline is not recommended unless other long-term treatment bronchodilators are unavailable or unaffordable (**Evidence B**).

Table 4.4. Initial Pharmacologic Management of COPD*

Patient Group	Recommended First Choice	Alternative Choice	Other Possible Treatments**
A	Short-acting anticholinergic prn *or* Short-acting $beta_2$-agonist prn	Long-acting anticholinergic *or* Long-acting $beta_2$-agonist *or* Short-acting $beta_2$-agonist and short-acting anticholinergic	Theophylline
B	Long-acting anticholinergic *or* Long-acting $beta_2$-agonist	Long-acting anticholinergic and long-acting $beta_2$-agonist	Short-acting $beta_2$-agonist *and/or* Short-acting anticholinergic Theophylline
C	Inhaled corticosteroid + long-acting $beta_2$-agonist *or* Long-acting anticholinergic	Long-acting anticholinergic and long-acting $beta_2$-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor *or* Long-acting $beta_2$-agonist and phosphodiesterase-4 inhibitor	Short-acting $beta_2$-agonist *and/or* Short-acting anticholinergic Theophylline
D	Inhaled corticosteroid + long-acting $beta_2$-agonist *and/or* Long-acting anticholinergic	Inhaled corticosteroid + long-acting $beta_2$-agonist and long-acting anticholinergic *or* Inhaled corticosteroid + long-acting $beta_2$-agonist and phosphodiesterase-4 inhibitor *or* Long-acting anticholinergic and long-acting $beta_2$-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor	Carbocysteine Short-acting $beta_2$-agonist *and/or* Short-acting anticholinergic Theophylline

*Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.
**Medications in this column can be used alone or in combination with other options in the Recommended First Choice and Alternative Choice columns.

Corticosteroids and Phosphodiesterase-4 Inhibitors — Recommendations

- There is no evidence to recommend a short-term therapeutic trial with oral corticosteroids in patients with COPD to identify those who will respond to inhaled corticosteroids or other medications.
- Long-term treatment with inhaled corticosteroids is recommended for patients with severe and very severe COPD and frequent exacerbations that are not adequately controlled by long-acting bronchodilators (**Evidence A**).
- Long-term monotherapy with oral corticosteroids is not recommended in COPD (**Evidence A**).
- Long-term monotherapy with inhaled corticosteroids is not recommended in COPD because it is less effective than the combination of inhaled corticosteroids with long-acting $beta_2$-agonists (**Evidence A**).
- Long-term treatment containing inhaled corticosteroids should not be prescribed outside their indications, due to the risk of pneumonia and the possibility of an increased risk of fractures following long-term exposure[540].
- The phosphodiesterase-4 inhibitor, roflumilast, may also be used to reduce exacerbations for patients with chronic bronchitis, severe and very severe COPD, and frequent exacerbations that are not adequately controlled by long-acting bronchodilators (**Evidence B**).

MONITORING AND FOLLOW-UP

Routine follow-up is essential in COPD. Lung function can be expected to worsen over time, even with the best available care. Symptoms and objective measures of airflow limitation should be monitored to determine when to modify therapy and to identify any complications that may develop. As at the initial assessment, follow-up visits should include a discussion of symptoms, particularly any new or worsening symptoms, and a physical examination. Comprehensive self-management or routine monitoring does not appear to show long term benefits in terms of quality of life or self efficacy over usual care alone in COPD patients in general practice[566].

Monitor Disease Progression and Development of Complications

Measurements. Decline in lung function is best tracked by spirometry performed at least once a year to identify patients whose lung function is declining quickly. Questionnaires such as the COPD Assessment Test *(CAT)*[124] can be performed every two to three months; trends and changes are more valuable than single measurements.

Symptoms. At each visit, inquire about changes in symptoms since the last visit, including cough and sputum, breathlessness, fatigue, activity limitation, and sleep disturbances.

Smoking Status. At each visit, determine current smoking status and smoke exposure; strongly encourage participation in programs to reduce and eliminate wherever possible exposure to COPD risk factors.

Monitor Pharmacotherapy and Other Medical Treatment

In order to adjust therapy appropriately as the disease progresses, each follow-up visit should include a discussion of the current therapeutic regimen. Dosages of various medications, adherence to the regimen, inhaler technique, effectiveness of the current regime at controlling symptoms, and side effects of treatment should be monitored. Treatment modifications should be recommended as appropriate with a focus on avoiding unnecessary polypharmacy.

At the individual patient level, measurements such as FEV_1 and questionnaires such as the CAT are useful but are not completely reliable, because the size of a clinically important response is smaller than between-assessment variability. For this reason, the following questions might be useful when deciding whether a patient has had a symptomatic response to treatment:

- Have you noticed a difference since starting this treatment?
- If you are better:
  - Are you less breathless?
  - Can you do more?
  - Can you sleep better?
  - Describe what difference it has made to you.
- Is that change worthwhile to you?

Monitor Exacerbation History

Evaluate the frequency, severity, and likely causes of any exacerbations[391]. Increased sputum volume, acutely worsening dyspnea, and the presence of purulent sputum should be noted. Specific inquiry into unscheduled visits to providers, telephone calls for assistance, and use of urgent or emergency care facilities is important. Severity of exacerbations can be estimated by the increased need for bronchodilator medication or corticosteroids and by the need for antibiotic treatment. Hospitalizations should be documented, including the facility, duration of stay, and any use of critical care or mechanical ventilatory support.

Monitor Comorbidities

Comorbidities are common in COPD, amplify the disability associated with COPD, and can potentially complicate its management. Until more integrated guidance about disease management for specific comorbid problems becomes available, the focus should be on identification and management of these individual problems in line with local treatment guidance (See also Chapter 6).

Surgery in the COPD Patient

Postoperative pulmonary complications are as important and common as postoperative cardiac complications and, consequently, are a key component of the increased risk posed by surgery in COPD patients[392]. The principal potential factors contributing to the risk include smoking, poor general health status, age, obesity, and COPD severity. A comprehensive definition of postoperative pulmonary complications should include only major pulmonary respiratory complications, namely lung infections, atelectasis and/or increased airflow limitation, which all potentially result in acute respiratory failure and aggravation of underlying COPD[291,393-395].

Increased risk of postoperative pulmonary complications in COPD patients may vary with the severity of COPD, although the surgical site is the most important predictor; risk increases as the incision approaches the diaphragm[394]. Most reports conclude that epidural or spinal anesthesia have a lower risk than general anesthesia, although the results are not totally uniform.

For lung resection, the individual patient's risk factors should be identified by careful history, physical examination, chest radiography, and pulmonary function tests. Although the value of pulmonary function tests remains contentious, there is consensus that all COPD candidates for lung resection should undergo a complete battery of tests, including spirometry with bronchodilator response, static lung volumes, diffusing capacity, and arterial blood gases at rest[396,397]. COPD patients at high risk for surgical complications due to poor lung function should undergo further lung function assessment, for example, tests of regional distribution of perfusion and exercise capacity[396,397].

The risk of postoperative complications from lung resection appears to be increased in patients with decreased predicted postoperative pulmonary function (FEV_1 or DL_{CO} < 30-40% predicted) or exercise capacity (peak VO_2 < 10 ml/kg/min or 35% predicted). The final decision to pursue surgery should be made after discussion with the surgeon, pulmonary specialist, primary clinician, and the patient. To prevent postoperative pulmonary complications, stable COPD patients clinically symptomatic and/or with limited exercise capacity should be treated intensively before surgery, with all the measures already well established for stable COPD patients who are not about to have surgery. Surgery should be postponed if an exacerbation is present.

CHAPTER

5

MANAGEMENT OF EXACERBATIONS

CHAPTER 5: MANAGEMENT OF EXACERBATIONS

KEY POINTS:

- *An exacerbation of COPD is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.*
- Exacerbations of COPD can be precipitated by several factors. The most common causes appear to be viral upper respiratory tract infections and infection of the tracheobronchial tree.
- The diagnosis of an exacerbation relies exclusively on the clinical presentation of the patient complaining of an acute change of symptoms (baseline dyspnea, cough, and/or sputum production) that is beyond normal day-to-day variation.
- The goal of treatment in COPD exacerbations is to minimize the impact of the current exacerbation and to prevent the development of subsequent exacerbations.
- Short-acting inhaled $beta_2$-agonists with or without short-acting anticholinergics are usually the preferred bronchodilators for treatment of an exacerbation.
- Systemic corticosteroids and antibiotics can shorten recovery time, improve lung function (FEV_1) and arterial hypoxemia (PaO_2), and reduce the risk of early relapse, treatment failure, and length of hospital stay.
- COPD exacerbations can often be prevented. Smoking cessation, influenza and pneumococcal vaccination, knowledge of current therapy including inhaler technique, and treatment with long-acting inhaled bronchodilators, with or without inhaled corticosteroids, and treatment with a phosphodiesterase-4 inhibitor are all interventions that reduce the number of exacerbations and hospitalizations.

DEFINITION

An exacerbation of COPD is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication[128-130].

Exacerbations of COPD are important events in the course of the disease because they:

- Negatively affect a patient's quality of life[144,391]
- Have effects on symptoms and lung function that take several weeks to recover from[398]
- Accelerate the rate of decline of lung function[399,400]
- Are associated with significant mortality, particularly in those requiring hospitalization
- Have high socioeconomic costs[401]

In-hospital mortality of patients admitted for a hypercapnic exacerbation with acidosis is approximately 10%[402]. Mortality reaches 40% at 1 year after discharge in those needing mechanical support, and all-cause mortality 3 years after hospitalization is as high as 49%[401-405]. Prevention, early detection, and prompt treatment of exacerbations are vital to reduce the burden of COPD[406].

Exacerbations of COPD can be precipitated by several factors. The most common causes appear to be respiratory tract infections (viral or bacterial). Bronchoscopic studies have shown that at least 50% of patients have bacteria in their lower airways during exacerbations of COPD[407-409], but a significant proportion of these patients also have bacteria colonizing their lower airways in the stable phase of the disease. On the other hand, there is some indication that the bacterial burden increases during some exacerbations of COPD[410-412], and that acquisition of bacterial strains that are new to the patient is associated with exacerbations of COPD[413]. Air pollution can also precipitate exacerbations of COPD[414-416]. However, the cause of about one-third of severe exacerbations of COPD cannot be identified. Some patients appear particularly prone to suffer exacerbations of COPD whereas others do not. Those reporting two or more exacerbations of COPD per year are often defined as "frequent exacerbators[132]," a phenotype that appears stable over time.

In addition to infections and exposure to pollutants, exacerbations of respiratory symptoms (especially dyspnea) in patients with COPD may be due to different mechanisms that may overlap in the same patients. Conditions that may mimic and/or aggravate exacerbations, including pneumonia, pulmonary embolism, congestive heart failure, cardiac arrhythmia, pneumothorax, and pleural effusion, need to be considered in the differential diagnosis and treated if present[128,291,398,417]. Interruption of maintenance therapy has also been shown to lead to exacerbations.

DIAGNOSIS

Currently, the diagnosis of an exacerbation relies exclusively on the clinical presentation of the patient complaining of an acute change of symptoms (baseline dyspnea, cough, and/or sputum production) that is beyond normal day-to-day variation. In the future, a biomarker or panel of biomarkers that allows a more precise etiologic diagnosis would be desirable.

ASSESSMENT

The assessment of an exacerbation is based on the patient's medical history and clinical signs of severity (**Tables 5.1** and **5.2**) and some laboratory tests, if available.

Table 5.1. Assessment of COPD Exacerbations: Medical History
• Severity of COPD based on degree of airflow limitation • Duration of worsening or new symptoms • Number of previous episodes (total/hospitalizations) • Comorbidities • Present treatment regimen • Previous use of mechanical ventilation

Table 5.2. Assessment of COPD Exacerbations: Signs of Severity
• Use of accessory respiratory muscles • Paradoxical chest wall movements • Worsening or new onset central cyanosis • Development of peripheral edema • Hemodynamic instability • Deteriorated mental status

The following tests may be considered to assess the severity of an exacerbation:

- *Pulse oximetry* is useful for tracking and/or adjusting supplemental oxygen therapy. The measurement of arterial blood gases is vital if the coexistence of acute or acute-on-chronic respiratory failure is suspected (PaO_2 < 8.0 kPa (60 mmHg) with or without $PaCO_2$ > 6.7 kPa (50 mmHg) breathing ambient air). Assessment of the acid-base status is necessary before initiating mechanical ventilation[291,418].
- *Chest radiographs* are useful in excluding alternative diagnoses.
- *An ECG* may aid in the diagnosis of coexisting cardiac problems.
- *Whole blood* count may identify polycythemia (hematocrit > 55%), anemia, or leukocytosis.
- The presence of *purulent sputum* during an exacerbation can be sufficient indication for starting empirical antibiotic treatment[114]. *Hemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* are the most common bacterial pathogens involved in an exacerbation[409]; in GOLD 3 and GOLD 4 patients *Pseudomonas aeruginosa* becomes important. If an infectious exacerbation does not respond to the initial antibiotic treatment, a sputum culture and an antibiotic sensitivity test should be performed[291].
- *Biochemical test abnormalities* including electrolyte disturbances and hyperglycemia can be associated with exacerbations. However, these abnormalities can also be due to associated comorbidities.

Spirometry is not recommended during an exacerbation because it can be difficult to perform and measurements are not accurate enough.

TREATMENT OPTIONS

Treatment Setting

The goals of treatment for COPD exacerbations are to minimize the impact of the current exacerbation and prevent the development of subsequent exacerbations[419]. Depending on the severity of an exacerbation and/or the severity of the underlying disease, an exacerbation can be managed in an outpatient or inpatient setting. More than 80% of exacerbations can be managed on an outpatient basis[132,143,214] with pharmacologic therapies including bronchodilators, corticosteroids, and antibiotics.

Table 5.3 shows the indications for hospital assessment and potential admission of a patient with a COPD exacerbation. When a patient comes to the emergency department the first actions are to provide supplemental oxygen therapy and to determine whether the exacerbation is life-threatening (**Table 5.4**). If so, the patient should be admitted to the ICU immediately. Otherwise, the patient may be managed in the emergency department or hospital as detailed in **Table 5.5**. In addition to pharmacologic therapy, hospital management of exacerbations includes respiratory support (oxygen therapy, ventilation) as detailed in **Table 5.5**.

Table 5.3. Potential Indications for Hospital Assessment or Admission*
• Marked increase in intensity of symptoms, such as sudden development of resting dyspnea • Severe underlying COPD • Onset of new physical signs (e.g., cyanosis, peripheral edema) • Failure of an exacerbation to respond to initial medical management • Presence of serious comorbidities (e.g., heart failure or newly occurring arrhythmias) • Frequent exacerbations • Older age • Insufficient home support

*Local resources need to be considered.

Pharmacologic Treatment

The three classes of medications most commonly used for exacerbations of COPD are bronchodilators, corticosteroids, and antibiotics.

Short-acting Bronchodilators. Although there are no controlled trials, short-acting inhaled $beta_2$-agonists with or without short-acting anticholinergics are usually the preferred bronchodilators for treatment

Table 5.4. Management of Severe but Not Life-Threatening Exacerbations*

- Assess severity of symptoms, blood gases, chest radiograph
- Administer supplemental oxygen therapy and obtain serial arterial blood gas measurement
- Bronchodilators:
  – Increase doses and/or frequency of short-acting bronchodilators
  – Combine short-acting $beta_2$-agonists and anticholinergics
  – Use spacers or air-driven nebulizers
- Add oral or intravenous corticosteroids
- Consider antibiotics (oral or occasionally intravenous) when signs of bacterial infection
- Consider noninvasive mechanical ventilation
- At all times:
  – Monitor fluid balance and nutrition
  – Consider subcutaneous heparin or low molecular weight heparin
  – Identify and treat associated conditions (e.g., heart failure, arrhythmias)
  – Closely monitor condition of the patient

**Local resources need to be considered.*

Table 5.5. Therapeutic Components of Hospital Management

RESPIRATORY SUPPORT
- Oxygen therapy
- Ventilatory support
  - Noninvasive ventilation
  - Invasive ventilation

PHARMACOLOGIC TREATMENT
- Bronchodilators
- Corticosteroids
- Antibiotics
- Adjunct therapies

of an exacerbation[290,291] (**Evidence C**). There are no clinical studies that have evaluated the use of inhaled long-acting bronchodilators (either $beta_2$-agonists or anticholinergics) with or without inhaled corticosteroids during an exacerbation. A systematic review of the route of delivery of short-acting bronchodilators found no significant differences in FEV_1 between metered-dose inhalers (with or without a spacer device) and nebulizers[420], although the latter can be more convenient for sicker patients. Intravenous methylxanthines (theophylline or aminophylline) are considered second-line therapy, only to be used in selected cases when there is insufficient response to short-acting bronchodilators[421-425] (**Evidence B**). Side effects of methylxanthines are significant and their beneficial effects in terms of lung function and clinical endpoints are modest and inconsistent[426,427].

Corticosteroids. Data from studies in secondary health care indicate that systemic corticosteroids in COPD exacerbations shorten recovery time, improve lung function (FEV_1) and arterial hypoxemia (PaO_2)[428-431] (**Evidence A**), and reduce the risk of early relapse, treatment failure[541], and length of hospital stay[428,430,432]. A dose of 40 mg prednisone per day for 5 days is recommended (**Evidence B**)[567], although there are insufficient data to provide firm conclusions concerning the optimal duration of corticosteroid therapy of acute exacerbations of COPD[542]. Therapy with oral prednisolone is preferable[433]. Nebulised budesonide alone may be an alternative (although more expensive) to oral corticosteroids in the treatment of exacerbations[429,434,435]. Nebulised magnesium as an adjuvant to salbutamol treatment in the setting of acute exacerbations of COPD has no effect on FEV_1[568].

Antibiotics. Although the infectious agents in COPD exacerbations can be viral or bacterial[273,436], the use of antibiotics in exacerbations remains controversial[567]. The uncertainties originate from studies that did not differentiate between bronchitis (acute or chronic) and COPD exacerbations, studies without placebo-control, and/or studies without chest X-rays in which it was unclear if patients had signs of pneumonia. There is evidence supporting the use of antibiotics in exacerbations when patients have clinical signs of a bacterial infection, e.g., increase in sputum purulence[114]. A systematic review of the very few available placebo-controlled studies has shown that antibiotics reduce the risk of short-term mortality by 77%, treatment failure by 53% and sputum purulence by 44%. This review supports antibiotics for only moderately or severely ill patients with COPD exacerbations with increased cough and sputum purulence[437,438]. In outpatients, sputum cultures are not feasible as they take too long (at least 2 days) and frequently do not give reliable results for technical reasons, i.e., more than 4 hours elapse between expectoration of sputum and analysis in the microbiology lab. Procalcitonin III, a marker that is specific for bacterial infections, may be of value in the decision to use antibiotics[439], but this test is expensive and thus not widely established. A study in COPD patients with exacerbations requiring mechanical ventilation (invasive or noninvasive) indicated that not giving antibiotics was associated with increased mortality and a greater incidence of secondary nosocomial pneumonia[440].

In summary, antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms – increase in dyspnea, sputum volume, and sputum purulence (**Evidence B**); have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms (**Evidence C**); or require mechanical ventilation (invasive or noninvasive) (**Evidence B**)[273,351]. The recommended length of antibiotic therapy is usually 5-10 days (**Evidence D**).

The choice of the antibiotic should be based on the local bacterial resistance pattern. Usually initial empirical treatment is an aminopenicillin with or without clavulanic acid, macrolide, or tetracycline. In patients with frequent exacerbations, severe airflow limitation[417,441], and/or exacerbations requiring mechanical ventilation[412], cultures from sputum or other materials from the lung should be performed, as gram-negative bacteria (e.g., *Pseudomonas species*) or resistant pathogens that are not sensitive to the above-mentioned antibiotics may be present. The route of administration (oral or intravenous) depends on the ability of the patient to eat and the pharmacokinetics of the antibiotic, although preferably antibiotics are given orally. Improvements in dyspnea and sputum purulence suggest clinical success.

Adjunct Therapies: Depending on the clinical condition of the patient, an appropriate fluid balance with special attention to the administration of diuretics, anticoagulants, treatment of comorbidities and nutritional aspects should be considered. At all times, health care providers should strongly enforce stringent measures against active cigarette smoking. Given that patients hospitalized because of exacerbations of COPD are at increased risk of deep vein thrombosis and pulmonary embolism[570,571], thromboprophylactic measures should be enhanced[572-574].

Respiratory Support

Oxygen therapy. This is a key component of hospital treatment of an exacerbation. Supplemental oxygen should be titrated to improve the patient's hypoxemia with a target saturation of 88-92%[442]. Once oxygen is started, arterial blood gases should be checked 30-60 minutes later to ensure satisfactory oxygenation without carbon dioxide retention or acidosis. Venturi masks (high-flow devices) offer more accurate and controlled delivery of oxygen than do nasal prongs but are less likely to be tolerated by the patient[291].

Ventilatory Support. Some patients need immediate admission to an intensive care unit (ICU) (**Table 5.6**). Admission of patients with severe exacerbations to intermediate or special respiratory care units may be appropriate if personnel, skills, and equipment exist to identify and manage acute respiratory failure successfully.

Ventilatory support in an exacerbation can be provided by either noninvasive (by nasal or facial mask) or invasive ventilation (by oro-tracheal tube or tracheostomy). Respiratory stimulants are not recommended for acute respiratory failure[290].

Noninvasive mechanical ventilation. The use of noninvasive mechanical ventilation (NIV) has increased significantly over time among patients hospitalized for acute exacerbations of COPD. NIV has been studied in randomized controlled trials showing a success rate of 80-85% [443-446,543]. NIV has been shown to improve acute respiratory acidosis (increases pH and decreases $PaCO_2$), decrease respiratory rate, work of breathing, severity of breathlessness, complications such as ventilator associated pneumonia, and length of hospital stay (**Evidence A**). More importantly, mortality and intubation rates are reduced by this intervention[444,447-449] (**Evidence A**). **Table 5.7** summarizes the indications for NIV[443].

Table 5.6. Indications for ICU Admission *

- Severe dyspnea that responds inadequately to initial emergency therapy
- Changes in mental status (confusion, lethargy, coma)
- Persistent or worsening hypoxemia (PaO_2 < 5.3 kPa, 40 mmHg) and/or severe/worsening respiratory acidosis (pH < 7.25) despite supplemental oxygen and noninvasive ventilation
- Need for invasive mechanical ventilation
- Hemodynamic instability—need for vasopressors

**Local resources need to be considered.*

Invasive mechanical ventilation. The indications for initiating invasive mechanical ventilation during an exacerbation are shown in **Table 5.8**, and include failure of an initial trial of NIV[450]. As experience is being gained with the generalized clinical use of NIV in COPD, several indications for invasive mechanical ventilation are being successfully treated with NIV, and in all but a few situations there is nothing to be lost by a trial of noninvasive ventilation[450].

Table 5.7. Indications for Noninvasive Mechanical Ventilation[291,445,451,452]

At least one of the following:

- Respiratory acidosis (arterial pH ≤ 7.35 and/or $PaCO_2$ ≥ 6.0 kPa, 45 mm Hg)
- Severe dyspnea with clinical signs suggestive of respiratory muscle fatigue, increased work of breathing, or both, such as use of respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces

Table 5.8. Indications for Invasive Mechanical Ventilation

- Unable to tolerate NIV or NIV failure
- Respiratory or cardiac arrest
- Respiratory pauses with loss of consciousness or gasping for air
- Diminished consciousness, psychomotor agitation inadequately controlled by sedation
- Massive aspiration
- Persistent inability to remove respiratory secretions
- Heart rate < 50 min^{-1} with loss of alertness
- Severe hemodynamic instability without response to fluids and vasoactive drugs
- Severe ventricular arrhythmias
- Life-threatening hypoxemia in patients unable to tolerate NIV

The use of invasive ventilation in very severe COPD patients is influenced by the likely reversibility of the precipitating event, patient's wishes, and availability of intensive care facilities. When possible, a clear statement of the patient's own treatment wishes—an advance directive or "living will"—makes these difficult decisions much easier to resolve. Major hazards include the risk of ventilator-acquired pneumonia (especially when multi-resistant organisms are prevalent), barotrauma, and failure to wean to spontaneous ventilation.

Contrary to some opinions, acute mortality among COPD patients with respiratory failure is lower than mortality among patients ventilated for non-COPD causes[453].

Despite this, there is evidence that patients who might otherwise survive may be denied admission to intensive care for intubation because of unwarranted prognostic pessimism[454]. A study of a large number of COPD patients with acute respiratory failure reported in-hospital mortality of 17-49%[403]. Further deaths were reported over the next 12 months, particularly among those patients who had poor lung function before invasive ventilation (FEV_1 < 30% predicted), had a non-respiratory comorbidity, or were housebound. Patients who did not have a previously diagnosed comorbidity, had respiratory failure due to a potentially reversible cause (such as an infection), or were relatively mobile and not using long-term oxygen did surprisingly well after ventilatory support.

Weaning or discontinuation from mechanical ventilation can be particularly difficult and hazardous in patients with COPD. The most influential determinant of mechanical ventilatory dependency in these patients is the balance between the respiratory load and the capacity of the respiratory muscles to cope with this load[455]. By contrast, pulmonary gas exchange by itself is not a major difficulty in patients with COPD[456-458]. Weaning patients from the ventilator can be a very difficult and prolonged process and the best method (pressure support or a T-piece trial) remains a matter of debate[459-461]. In COPD patients that fail extubation, NIV facilitates weaning, prevents reintubation, and reduces mortality[451,462]. Early NIV after extubation reduces the risk of respiratory failure and lowers 90-day mortality in patients with hypercapnia during a spontaneous breathing trial[457,462].

HOSPITAL DISCHARGE AND FOLLOW-UP

Insufficient clinical data exist to establish the optimal duration of hospitalization in individual patients with an exacerbation of COPD[463-465], although units with more respiratory consultants and better organized care have lower mortality and reduced length of hospital stay following admission for an exacerbation[466]. In the hospital prior to discharge, patients should start long-acting bronchodilators, either $beta_2$-agonists and/or anticholinergics with or without inhaled corticosteroids. Consensus and limited data support the discharge criteria listed in **Table 5.9**. **Table 5.10** provides a checklist of items to assess at time of discharge

Table 5.9. Discharge Criteria

- Able to use long acting bronchodilators, either $beta_2$-agonists and/or anticholinergics with or without inhaled corticosteroids
- Inhaled short-acting $beta_2$-agonist therapy is required no more frequently than every 4 hrs
- Patient, if previously ambulatory, is able to walk across room
- Patient is able to eat and sleep without frequent awakening by dyspnea
- Patient has been clinically stable for 12-24 hrs
- Arterial blood gases have been stable for 12-24 hrs
- Patient (or home caregiver) fully understands correct use of medications
- Follow-up and home care arrangements have been completed (e.g., visiting nurse, oxygen delivery, meal provisions)
- Patient, family, and physician are confident that the patient can manage successfully at home

Table 5.10. Checklist of Items to Assess at Time of Discharge from Hospital

- Assurance of effective home maintenance pharmacotherapy regimen
- Reassessment of inhaler technique
- Education regarding role of maintenance regimen
- Instruction regarding completion of steroid therapy and antibiotics, if prescribed
- Assess need for long-term oxygen therapy
- Assure follow-up visit in 4-6 weeks
- Provide a management plan for comorbidities and their follow-up

Table 5.11. Items to Assess at Follow-Up Visit 4-6 Weeks After Discharge from Hospital

- Ability to cope in usual environment
- Measurement of FEV_1
- Reassessment of inhaler technique
- Understanding of recommended treatment regimen
- Reassess need for long-term oxygen therapy and/or home nebulizer
- Capacity to do physical activity and activities of daily living
- CAT or mMRC
- Status of comorbidities

and **Table 5.11** shows items to assess at follow-up 4 to 6 weeks after discharge from the hospital. Thereafter, follow-up is the same as for stable COPD: supervise smoking cessation, monitor the effectiveness of each medication, and monitor changes in spirometric parameters[467]. Prior hospital admission, oral corticosteroids, use of long-term oxygen therapy, poor health-related quality of life, and lack of routine physical activity have been found to be predictive of readmission[468].

Home visits by a community nurse may permit earlier discharge of patients hospitalized with an exacerbation without increasing readmission rates[291,469-472]. Use of a written action plan increases appropriate therapeutic interventions for an exacerbation, an effect that does not decrease health-care resource utilization[473] (**Evidence B**) but may shorten recovery time[474].

For patients who are hypoxemic during an exacerbation, arterial blood gases and/or pulse oximetry should be evaluated prior to hospital discharge and in the following 3 months. If the patient remains hypoxemic, long-term supplemental oxygen therapy may be required.

HOME MANAGEMENT OF EXACERBATIONS

The risk of dying from an exacerbation of COPD is closely related to the development of respiratory acidosis, the presence of significant comorbidities, and the need for ventilatory support[402]. Patients lacking these features are not at high risk of dying. Four randomized clinical trials have shown that nurse-administered home care (also known as "hospital-at-home" care) represents an effective and practical alternative to hospitalization in selected patients with exacerbations of COPD without acidotic respiratory failure[467-470,544] (**Evidence A**). However, the exact criteria for this approach as opposed to hospital treatment remain uncertain and will vary by health care setting[469,470]. Treatment recommendations are the same for hospitalized patients. Supported self-management had no effect on time to first readmission or death with COPD[545]. Accumulating data from a variety of studies indicate that telehealth in any of its current forms has not shown benefits for patients with COPD; thus, telehealth is not recommended for use with COPD patients[575-577].

PREVENTION OF COPD EXACERBATIONS

COPD exacerbations can often be prevented. Smoking cessation, influenza and pneumococcal vaccines, knowledge of current therapy including inhaler technique, and treatment with long-acting inhaled bronchodilators, with or without inhaled corticosteroids, and possibly phosphodiesterase-4 inhibitors, are all therapies that reduce the number of exacerbations and hospitalizations[133,134,195,214,264,266]. Early outpatient pulmonary rehabilitation after hospitalization for an exacerbation is safe and results in clinically significant improvements in exercise capacity and health status at 3 months[475]. Patients should be encouraged to maintain physical activity, and anxiety, depression and social problems should be discussed. Principal caregivers should be identified if the patient has a significant persisting disability.

CHAPTER

6

COPD AND COMORBIDITIES

CHAPTER 6: COPD AND COMORBIDITIES

KEY POINTS:

- COPD often coexists with other diseases (comorbidities) that may have a significant impact on prognosis.
- In general, the presence of comorbidities should not alter COPD treatment and comorbidities should be treated as if the patient did not have COPD.
- Cardiovascular disease is a major comorbidity in COPD and probably both the most frequent and most important disease coexisting with COPD.
- Osteoporosis and depression are also major comorbidities in COPD, are often under-diagnosed, and are associated with poor health status and prognosis.
- Lung cancer is frequently seen in patients with COPD and has been found to be the most frequent cause of death in patients with mild COPD.

INTRODUCTION

COPD often coexists with other diseases (comorbidities) that may have a significant impact on prognosis[100,135,142,476,578]. Some of these arise independently of COPD whereas others may be causally related, either with shared risk factors or by one disease actually increasing the risk of another. It is possible that features of COPD, such as systemic inflammation, are shared with other diseases and as such this mechanism represents a link between COPD and some of its comorbidities[477]. This risk of comorbid disease can be increased by the sequelae of COPD; e.g., reduced physical activity. Whether or not COPD and comorbid diseases are related, management of the COPD patient must include identification and treatment of its comorbidities. Importantly, comorbidities with symptoms also associated with COPD may be overlooked; e.g., heart failure and lung cancer (breathlessness) or depression (fatigue and reduced physical activity). Frequent and treatable comorbidities should be prioritized.

Comorbidities are common at any severity of COPD[131] and the differential diagnosis can often be difficult. For example, in a patient with both COPD and heart failure an exacerbation of COPD may be accompanied by worsening of heart failure.

Below is a brief guide to management of COPD and some comorbidities in stable disease. The recommendations may be insufficient for the management of all patients and cannot substitute for the use of guidelines for the management of each comorbidity.

Cardiovascular Disease (CVD)

CVD is a major comorbidity in COPD and probably both the most frequent and most important disease coexisting with COPD[135,477]. Four separate entities within CVD will be considered: ischemic heart disease, heart failure, atrial fibrillation and hypertension.

Ischemic Heart Disease (IHD): IHD is increased in COPD, to some extent because of an unfavourable IHD risk profile in COPD patients[478,479]. There is evidence that myocardial injury is overlooked and IHD is therefore under-diagnosed in COPD patients[480].

Treatment of IHD in patients with COPD: IHD should be treated according to usual IHD guidelines, as there is no evidence that IHD should be treated differently in the presence of COPD. In a significant proportion of patients with IHD a beta-blocker will be indicated, either to treat angina or after a myocardial infarction. Treatment with selective $beta_1$-blockers is considered safe[481,546,579,580] but this is based on relatively few short-term studies. The benefits of selective $beta_1$-blockers when indicated in IHD are, however, considerably larger than the potential risks associated with treatment, even in patients with severe COPD.

Treatment of COPD in patients with IHD: COPD should be treated as usual as there is no evidence that COPD should be treated differently in the presence of IHD. This statement is based on findings from large long-term studies in COPD alone[195,214,482], but no large long-term studies exist in patients with both COPD and IHD. Although no studies on COPD medications in patients with unstable angina exist, it seems reasonable to avoid especially high doses of beta-agonists.

Heart Failure (HF): Heart failure is a common comorbidity in COPD. Roughly 30% of patients with stable COPD will have some degree of HF[483], and worsening of HF is a significant differential diagnosis to an exacerbation of COPD. Approximately 30% of patients in a HF clinic have COPD[484], and comorbid COPD is often be the cause of admission for acute HF[485] – with significant implications for prognosis as FEV_1 is a strong predictor of mortality in HF[486]. HF, COPD and asthma may be confused because of the common cardinal symptom of breathlessness, and caution is warranted for diagnosis and management of these comorbidities.

Treatment of HF in patients with COPD: HF should be treated according to usual HF guidelines as there is no evidence that HF should be treated differently in the presence of COPD. Treatment with selective beta$_1$-blockers has a significant impact on survival in HF and the presence of COPD is the most significant reason for patients not receiving sufficient therapy[487]. However, as in IHD, treatment with selective beta$_1$-blockers is considered safe for heart failure patients who also have COPD[481,579,580]. Studies have shown that treatment with bisoprolol in HF with concomitant COPD decreased FEV_1 but without deleterious effects on symptoms and quality of life[488] and that a selective beta$_1$-blocker is indeed preferable to a non-selective beta-blocker in HF with COPD[489]. In a study of patients with moderate-severe airflow limitation and heart failure (NYHA II), treatment with bisoprolol and carvedilol was well tolerated and beneficial effects on lung function were seen. Bisoprolol was superior to carvedilol on respiratory parameters[547]. The benefits of selective beta$_1$-blocker treatment in HF clearly outweigh any potential risk associated with treatment even in patients with severe COPD.

Treatment of COPD in patients with HF: COPD should be treated as usual as there is no direct evidence that COPD should be treated differently in the presence of HF. As for IHD this statement is based on findings from large long-term studies in patients with HF and comorbid COPD[195,214,482]. An observational study found an increased risk of death and hospital admission among patients with HF treated with inhaled beta-agonists[490], possibly indicating a need for close follow-up of patients with severe HF who are on this treatment for COPD.

Atrial Fibrillation (AF): Atrial fibrillation is the most frequent cardiac arrhythmia and COPD patients have an increased incidence of AF[491]. COPD with AF presents a challenge to clinicians because of the breathlessness and disability resulting from their coexistence.

Treatment of AF in patients with COPD: AF should be treated according to usual AF guidelines, as there is no evidence that patients with COPD should be treated differently from all other patients. If beta-blockers are used, beta$_1$-selective drugs are preferred (see considerations under IHD and HF above).

Treatment of COPD in patients with AF: COPD should be treated as usual; however, there are no good data on the use of COPD medication in patients with AF and these patients have often been excluded from clinical trials. It is a clinical impression that care should be taken when using high doses of beta$_2$-agonists as this can make appropriate heart rate control difficult.

Hypertension: Hypertension is likely to be the most frequently occurring comorbidity in COPD and has implications for prognosis[477].

Treatment of hypertension in patients with COPD: Hypertension should be treated according to usual hypertension guidelines, as there is no evidence that hypertension should be treated differently in the presence of COPD. The role of treatment with selective beta-blockers is less prominent in recent hypertension guidelines; if these are used in patients with COPD, a selective beta$_1$-blocker should be chosen.

Treatment of COPD in patients with hypertension: COPD should be treated as usual as there is no direct evidence that COPD should be treated differently in the presence of hypertension.

Osteoporosis

Osteoporosis is a major comorbidity in COPD[135,477], is often under-diagnosed[492] and is associated with poor health status and prognosis. Osteoporosis may be more closely associated with emphysema than other subgroups of COPD[493]. Osteoporosis is more often associated with decreased body mass index[494] and low fat-free mass[495].

Treatment of osteoporosis in patients with COPD: Osteoporosis should be treated according to usual osteoporosis guidelines. There is no evidence that osteoporosis should be treated differently in the presence of COPD.

Treatment of COPD in patients with osteoporosis: COPD should be treated as usual, as there is no evidence that stable COPD should be treated differently in the presence of osteoporosis. Inhaled triamcinolone was associated with increased loss of bone mass in the Lung Health Study II[496], whereas this was not the case for inhaled budesonide in the EUROSCOP trial[175] or for inhaled fluticasone propionate in the TORCH trial[250]. An association between inhaled corticosteroids and fractures has been found in pharmaco-epidemiological studies; however, these studies have not fully taken severity of COPD or exacerbations and their treatment into account.

Systemic corticosteroids significantly increase the risk of osteoporosis and recurrent courses of systemic corticosteroids for COPD exacerbations should be avoided if possible.

Anxiety and Depression

Anxiety and depression are major comorbidities in COPD[117,497-499] and both are associated with a poor prognosis[498,500]. Both are often associated with younger age, female gender, smoking, lower FEV_1, cough, higher SGRQ score, and a history of cardiovascular disease[117,499].

Treatment of anxiety and depression in patients with COPD: Both disorders should be treated according to usual guidelines, as there is no evidence that anxiety and depression should be treated differently in the presence of COPD. Given the large number of patients who have both depression and COPD, more research on management of depression in COPD patients is needed[501].

Treatment of COPD in patients with anxiety and depression: COPD should be treated as usual as there is no evidence that stable COPD should be treated differently in the presence of anxiety and depression. The potential impact of pulmonary rehabilitation should be stressed as studies have found that physical exercise has a beneficial effect on depression in general[502].

Lung Cancer

Lung cancer is frequently seen in patients with COPD and has been found to be the most frequent cause of death in patients with mild COPD[217].

Treatment of lung cancer in patients with COPD: Lung cancer should be treated according to usual lung cancer guidelines, as there is no evidence that lung cancer should be treated differently in the presence of COPD. However, often the reduced lung function of COPD patients will be a factor limiting surgical intervention for lung cancer.

Treatment of COPD in patients with lung cancer: COPD should be treated as usual as there is no evidence that stable COPD should be treated differently in the presence of lung cancer.

Infections

Serious infections, especially respiratory infections, are frequently seen in patients with COPD[503].

Treatment of infections in patients with COPD: Macrolide antibiotics increase the serum concentration of theophylline. Apart from this, there is no evidence that infections should be treated differently in the presence of COPD. However, repeat courses of antibiotics for exacerbations may increase the risk for the presence of antibiotic resistant bacterial strains and more extensive cultures of serious infections may be warranted.

Treatment of COPD in patients with infections: COPD should be treated as usual as there is no evidence that stable COPD should be treated differently in the presence of infections. In patients who develop repeated pneumonias while on inhaled corticosteroids, this medication may be stopped in order to observe whether this medication could be the cause of repeated infections.

Metabolic Syndrome and Diabetes

Studies have shown that the presence of metabolic syndrome and manifest diabetes are more frequent in COPD and the latter is likely to impact on prognosis[142].

Treatment of diabetes in patients with COPD: Diabetes should be treated according to usual guidelines for diabetes, as there is no evidence that diabetes should be treated differently in the presence of COPD. However, for patients with severe COPD, it is not advised to aim for a body mass index (BMI) less than 21 kg/m^2.

Treatment of COPD in patients with diabetes: COPD should be treated as usual as there is no evidence that stable COPD should be treated differently in the presence of diabetes.

Bronchiectasis

Persistent airflow obstruction is a recognized feature of some patients with a primary diagnosis of bronchiectasis. However with increasing use of computed tomography in the assessment of patients with COPD, the presence of previously unrecognized radiographic bronchiectasis is being identified[581]. This ranges from mild tubular bronchiectasis to more severe varicose change, although cystic bronchiectasis is uncommon. Whether this radiological change has the same impact as patients with a primary diagnosis of bronchiectasis remains unknown at present, although it is associated with longer exacerbations[582] and increased mortality[583].

Treatment of bronchiectasis in patients with COPD: Treatment should be along conventional lines for bronchiectasis with the addition of usual COPD strategies where indicated. Whether prevention of exacerbations requires more long-term use of oral or inhaled antibiotics rather than bronchodilator or inhaled corticosteroid therapy remains unknown.

Treatment of COPD in patients with bronchiectasis: COPD should be treated as usual, although some patients may need more aggressive and prolonged antibiotic therapy.

CHAPTER

7

Asthma and COPD Overlap Syndrome (ACOS)

CHAPTER 7: ASTHMA COPD OVERLAP SYNDROME (ACOS) BACKGROUND SUMMARY

(A chapter on the diagnosis of Asthma and COPD Overlap Syndrome (ACOS) is in preparation by the Science Committees of the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD). It is expected to be available with the release of the GINA 2014 document Global Strategy for Asthma Management and Prevention in the Spring 2014. A brief background summary is provided in this 2014 GOLD update; the full chapter with references will be posted on the GOLD website when it is available, and will also appear in full in the Appendix of the 2015 GOLD update.)

The differential diagnosis in patients with respiratory symptoms varies by age. In children and young adults, once infectious disease and non-respiratory conditions (e.g. congenital heart disease, vocal cord dysfunction) have been excluded, the most likely chronic airway disease is asthma. In adults (usually after the age of 40 years) COPD becomes more common, and distinguishing asthma with chronic airflow limitation from COPD becomes problematic.

A significant proportion of patients who present with symptoms of a chronic airways disease have features of both asthma and COPD. Several diagnostic terms, most including the word "overlap", have been applied to such patients and the topic has been extensively reviewed. However, there is no generally agreed term or defining features for this category of chronic airflow limitation, although a definition based upon consensus has been published for overlap in patients with existing COPD.

In spite of these uncertainties, several studies have shown that patients with features of both asthma and COPD experience frequent exacerbations, have poor quality of life, a more rapid decline in lung function and high mortality, and consume a disproportionate amount of healthcare resources. In these reports, the proportion of patients with features of both asthma and COPD has varied between 15 and 55%, depending on the inclusion criteria used. Concurrent doctor-diagnosed asthma and COPD has been reported in between 15 and 20% of patients.

This document about diagnosis of patients with chronic airways disease has been developed by the Science Committees of both GINA and GOLD, based on a detailed review of available literature and consensus. It provides an approach to distinguishing between asthma, COPD and the overlap of asthma and COPD, for which the term Asthma COPD Overlap Syndrome (ACOS) is proposed. Rather than attempting a definition, features that identify and characterize ACOS are presented, using a syndromic approach that ascribes equal weight to features of asthma and COPD. The document also includes a simple approach to the initial management of such patients. The primary objective of this approach is to inform clinical practice, but it is acknowledged that within this description of ACOS will lie a number of phenotypes that may in due course be identified by more detailed characterization on the basis of clinical, pathophysiological and genetic identifiers.

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