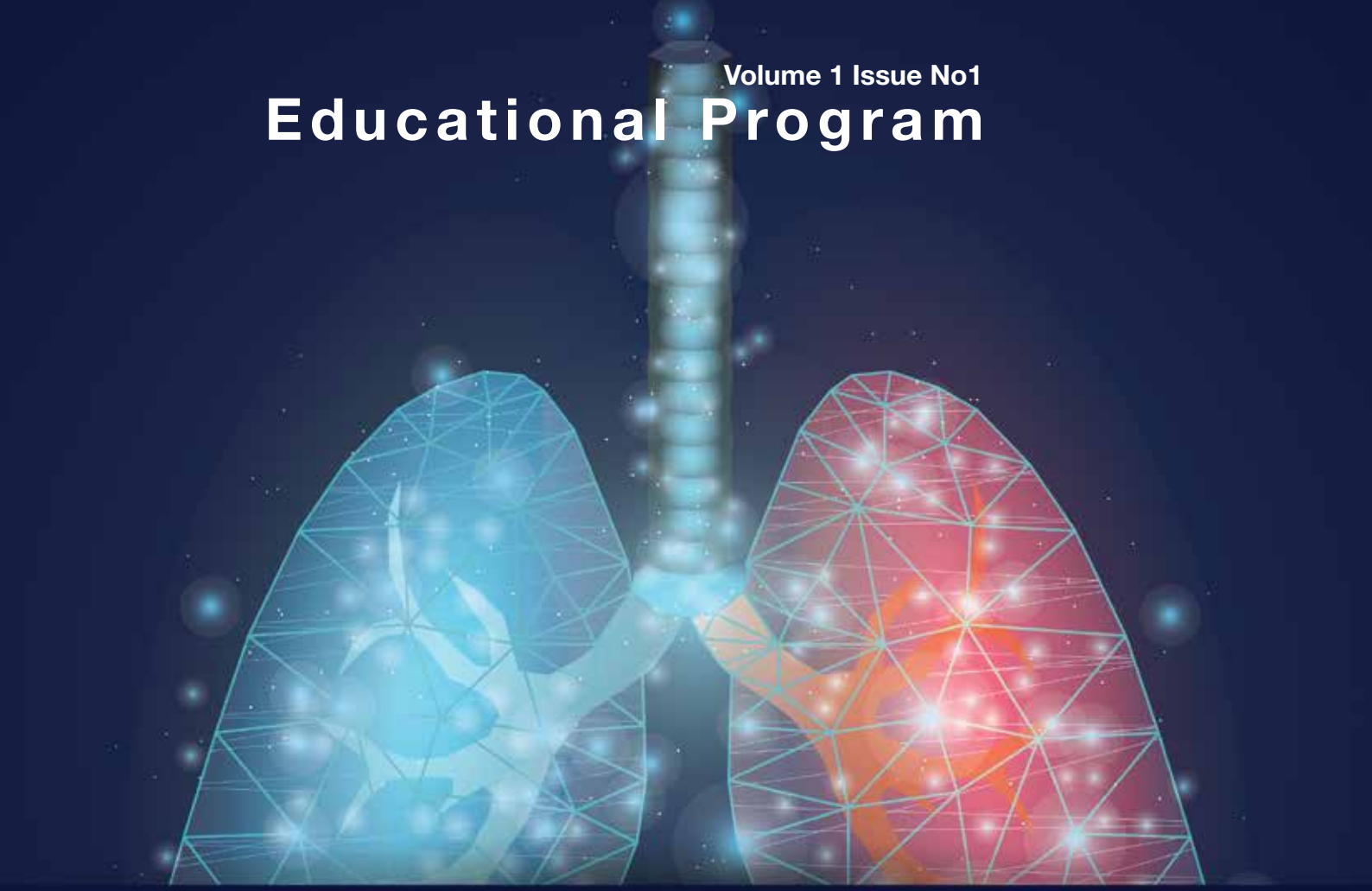
Volume 1 Issue No1

Educational Program

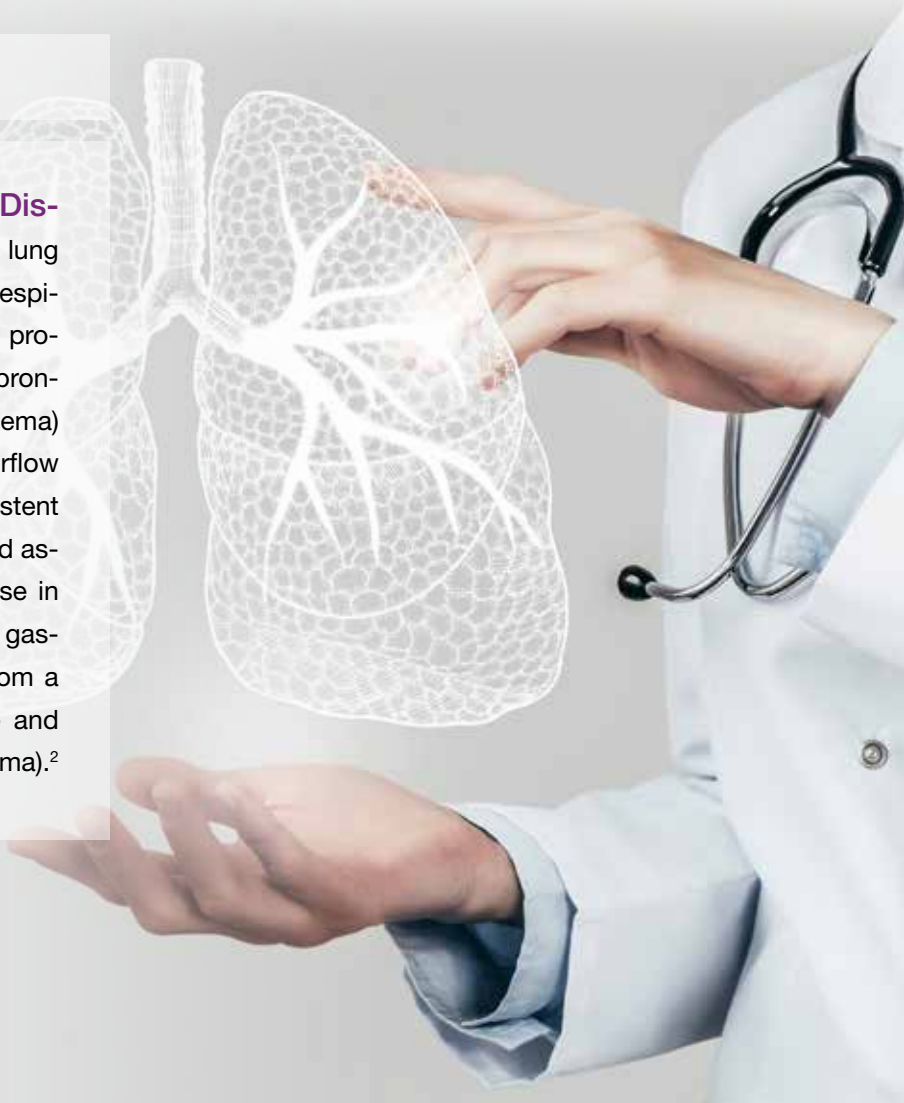


Faculty©

Chronic Obstructive Pulmonary Disease

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction.[1] COPD is characterized by persistent airflow limitation that is usually progressive and associated with a chronic inflammatory response in the airways and lungs to noxious particles or gases. The persistent airflow limitation results from a combination of diffuse small airway disease and destruction of the lung parenchyma (emphysema).[2]



The main aim of defining phenotypes in COPD patients is:

a. To identify those who could respond to specific treatments

b. To provide prognostic information

c. To provide multi-dimensional phenotyping

d. Both a and b

e. Both a and c

Correct Answer:

d **Both a and b**

The main aim of defining phenotypes in COPD patients is to identify those who could respond to specific treatments and to provide prognostic information. Most of the approaches to COPD phenotyping have focused at single level rather than multi-level to provide multi-dimensional phenotyping.

Source: Yousuf A, McAuley H, Elneima O, Brightling CE. The different phenotypes of COPD. Br Med Bull. 2021 Mar 25;137(1):82-97.

COPD is a common, preventable and treatable condition that is characterized by persistent respiratory symptoms and airflow limitation. It is a heterogeneous and complex disease associated with significant morbidity, mortality and healthcare expense.[3]

The main aim of defining phenotypes in COPD patient is to identify those who could respond to specific treatments and to provide prognostic information. Most of the approaches to COPD phenotyping have focused at single level rather than multi-level to provide multi-dimensional phenotyping. For example, at a whole person level patients can be characterized based on their degree of breathlessness or chronic productive cough. At organ level, patients can be characterized based on radiological findings (e.g. emphysematous changes in emphysema). At tissue level, patients can be characterized as eosinophilic or non-eosinophilic phenotype based on sputum or blood eosinophil count.[3]

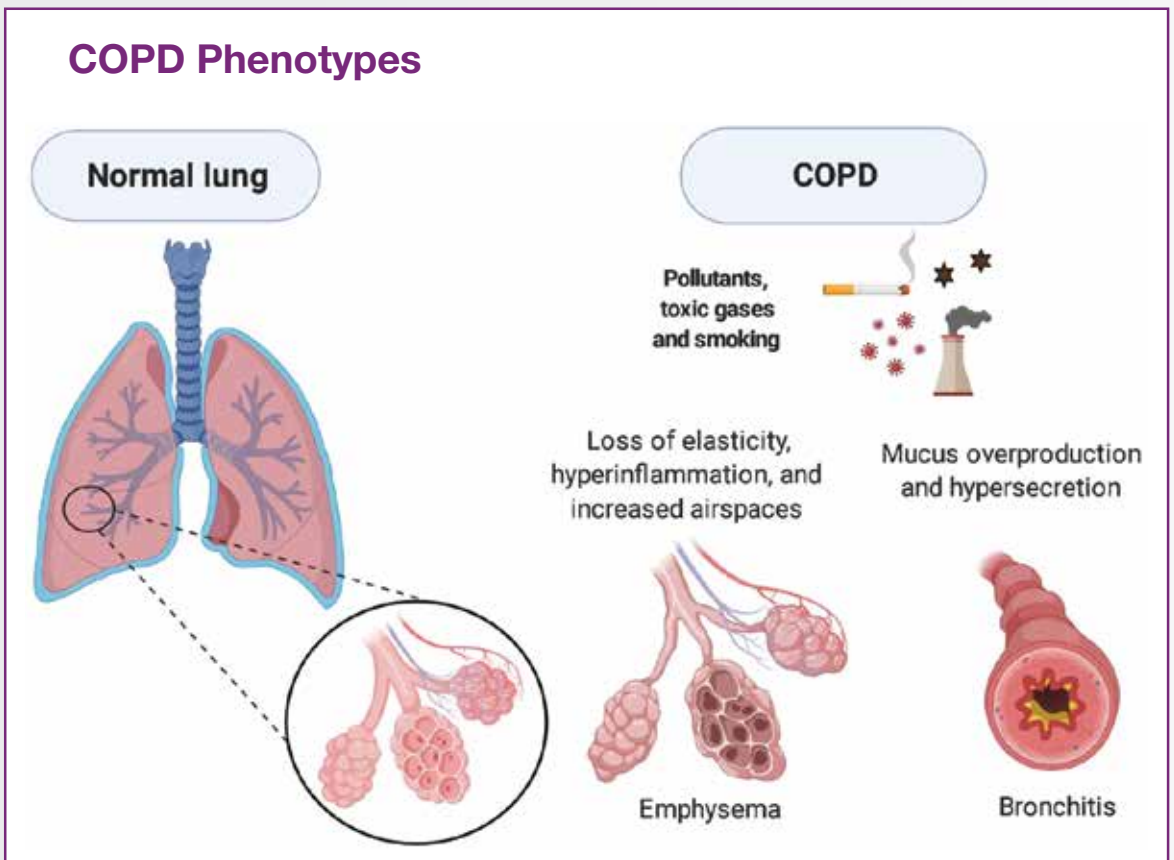


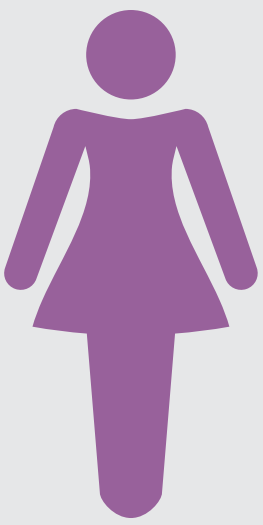
Figure 1. Morphological differences exist between a normal lung and a lung with COPD. In addition, lungs with COPD can present two different characteristics: emphysema, which promotes alveolar destruction and consequent reduction in lung function, and bronchitis, which increases mucus production, narrowing airways and reducing air flow. (From: Rodrigues SO, et al. Pharmaceuticals (Basel). 2021).

Sex as a Factor in COPD Heterogeneity

COPD has historically been considered a disease of older men, but its prevalence among women has been increasing. This change is due to the narrowing gap in gender disparities in smoking prevalence in high-income countries and greater likelihood of biomass exposure among women in low-income nations.[4]

Thus, **COPD now affects men and women almost equally**. However, female smokers who visit a physician are less likely than male smokers to be diagnosed with COPD, to receive spirometry testing, or to be referred to a pulmonologist. Sex differences in lung size are present throughout childhood and adolescence and persist into adulthood. On CT imaging, female smokers exhibit higher wall area percentage compared with male smokers, but lower luminal area, internal diameter, and airway thickness.[4]

This sex difference in airway dimensions may explain differing susceptibility to disease and phenotypic presentation:[4]



01 **Women** appear to be more susceptible to tobacco because they have more severe disease despite lower cumulative tobacco consumption, earlier onset of COPD, and faster decline in lung function

02 **Female sex hormones** may increase metabolism of cigarette smoke (CS) to generate oxidative stress and thus may contribute to greater airway injury.

Postmenopausal women may have faster rates of lung function decline

03 **The role of estrogen and progesterone** is unclear, and hormone replacement therapy has not been consistently associated with COPD risk

04 **In terms of phenotypic presentation,** women with COPD suffer disproportionately from higher levels of anxiety, depression, and worse dyspnea and symptom-related quality of life for the same degree of lung function impairment

Yet, they may report lower prevalence of other symptoms, such as cough and sputum production

Epidemiology / Burden of COPD

Published studies from high-income countries have reported a large variation in prevalence and incidence of COPD, both within a country and also among different countries. These variations are likely due to inherent population differences between geographic regions, but also could be related to a host of factors, including the sampling method, the specific populations studied, and the multitude of criteria used to define COPD.[5]

Safiri et al report the prevalence, deaths, and disability-adjusted life-years (DALYS) associated with COPD, and the attributable risk factors by age, sex, and sociodemographic index in 204 countries and territories from 1990 to 2019.[6] The Global Burden of Disease 2019 study estimated the burden of 369 diseases and injuries and 87 risk factors from 1990 to 2019 in 204 countries and territories and 21 regions.[7]

The global Burden of Disease 2019 showed that in 2019, COPD ranked within the top 10 causes of DALYS) in people aged 50–74 years and in those aged 75 years and older.[7] Low-income and middle-income countries (LIMICs) accounted for 62.6% of the global burden of COPD and this share is likely to increase sharply over the coming decades due to ageing populations and less successful tobacco and air pollution control.[7]

In 2019, the global **prevalence of COPD** among people aged 30-79 years was 10·3% (95% CI 8.2–12.8) using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) case definition, which translates to 391·9 million people (95% CI 312.6–487.9), and 7.6% (5.8–10.1) using the lower limit of normality (LLN) definition, which translates to 292.0 million people (219.8–385.6). Using the GOLD definition, Adeloye et al estimated that 391·9 million (95% CI 312.6–487.9) people aged 30–79 years had COPD worldwide in 2019, with most (315.5 million [246.7–399.6]; 80.5%) living in LMICs. The overall prevalence of GOLD-COPD among people aged 30–79 years was the highest in the Western Pacific region (11.7% [95% CI 9.3–14.6]) and lowest in the region of the Americas (6.8% [95% CI 5.6–8.2]). Globally, male sex (OR 2.1 [95% CI 1.8–2.3]), smoking (current smoker 3.2 [2.5–4.0]; ever smoker 2.3 [2.0–2.5]), body-mass index of less than 18·5 kg/m^2 (2.2 [1.7–2.7]), biomass exposure (1.4 [1.2–1.7]), and occupational exposure to dust or smoke (1.4 [1.3–1.6]) were all substantial risk factors for COPD.[7]

In the same year, COPD caused 3.22 million deaths, while the number of deaths rose by 17.5% between 2007 and 2017. The main burden of mortality from COPD is seen in Latin America, sub-Saharan Africa, India, China, and Southeast Asia.[8]

LMICs account for more than three-quarters of global COPD cases. High-income countries (HICs) still have higher prevalence than LMICs, which might be explained by differences in age distribution between populations. With increased life expectancy in the majority of LMICs, the prevalence of COPD in these countries is set to increase. With limited health information systems and clinical and research capacities, the likelihood of an underestimation in these settings cannot be ruled out. These findings highlight the need to prioritize actions to tackle COPD in LMICs to achieve significant reductions in the global burden of COPD.[7]

A All ages

Leading causes 1990	Percentage of DALYs 1990	Leading causes 2019	Percentage of DALYs 2019	Percentage change in number of DALYs, 1990–2019	Percentage change in age-standardised DALY rate, 1990–2019
1 Neonatal disorders	10·6 (9·9 to 11·4)	1 Neonatal disorders	7·3 (6·4 to 8·4)	−32·3 (−41·7 to −20·8)	−32·6 (−42·1 to −21·2)
2 Lower respiratory infections	8·7 (7·6 to 10·0)	2 Ischaemic heart disease	7·2 (6·5 to 7·9)	50·4 (39·9 to 60·2)	−28·6 (−33·3 to −24·2)
3 Diarrhoeal diseases	7·3 (5·9 to 8·8)	3 Stroke	5·7 (5·1 to 6·2)	32·4 (22·0 to 42·2)	−35·2 (−40·5 to −30·5)
4 Ischaemic heart disease	4·7 (4·4 to 5·0)	4 Lower respiratory infections	3·8 (3·3 to 4·3)	−56·7 (−64·2 to −47·5)	−62·5 (−69·0 to −54·9)
5 Stroke	4·2 (3·9 to 4·5)	5 Diarrhoeal diseases	3·2 (2·6 to 4·0)	−57·5 (−66·2 to −44·7)	−64·6 (−71·7 to −54·2)
6 Congenital birth defects	3·2 (2·3 to 4·8)	6 COPD	2·9 (2·6 to 3·2)	25·6 (15·1 to 46·0)	−39·8 (−44·9 to −30·2)
7 Tuberculosis	3·1 (2·8 to 3·4)	7 Road injuries	2·9 (2·6 to 3·0)	2·4 (−6·9 to 10·8)	−31·0 (−37·1 to −25·4)
8 Road injuries	2·7 (2·6 to 3·0)	8 Diabetes	2·8 (2·5 to 3·1)	147·9 (135·9 to 158·9)	24·4 (18·5 to 29·7)
9 Measles	2·7 (0·9 to 5·6)	9 Low back pain	2·5 (1·9 to 3·1)	46·9 (43·3 to 50·5)	−16·3 (−17·1 to −15·5)
10 Malaria	2·5 (1·4 to 4·1)	10 Congenital birth defects	2·1 (1·7 to 2·6)	−37·3 (−50·6 to −12·8)	−40·0 (−52·7 to −17·1)
11 COPD	2·3 (1·9 to 2·5)	11 HIV/AIDS	1·9 (1·6 to 2·2)	127·7 (97·3 to 171·7)	58·5 (37·1 to 89·2)
12 Protein-energy malnutrition	2·0 (1·6 to 2·7)	12 Tuberculosis	1·9 (1·7 to 2·0)	−41·0 (−47·2 to −33·5)	−62·8 (−66·6 to −58·0)
13 Low back pain	1·7 (1·2 to 2·1)	13 Depressive disorders	1·8 (1·4 to 2·4)	61·1 (56·9 to 65·0)	−1·8 (−2·9 to −0·8)
14 Self-harm	1·4 (1·2 to 1·5)	14 Malaria	1·8 (0·9 to 3·1)	−29·4 (−56·9 to 6·6)	−37·8 (−61·9 to −6·2)
15 Cirrhosis	1·3 (1·2 to 1·5)	15 Headache disorders	1·8 (0·4 to 3·8)	56·7 (52·4 to 62·1)	1·1 (−4·2 to 2·9)
16 Meningitis	1·3 (1·1 to 1·5)	16 Cirrhosis	1·8 (1·6 to 2·0)	33·0 (22·4 to 48·2)	−26·8 (−32·5 to −19·0)
17 Drowning	1·3 (1·1 to 1·4)	17 Lung cancer	1·8 (1·6 to 2·0)	69·1 (53·1 to 85·4)	−16·2 (−24·0 to −8·2)
18 Headache disorders	1·1 (0·2 to 2·4)	18 Chronic kidney disease	1·6 (1·5 to 1·8)	93·2 (81·6 to 105·0)	6·3 (0·2 to 12·4)
19 Depressive disorders	1·1 (0·8 to 1·5)	19 Other musculoskeletal	1·6 (1·2 to 2·1)	128·9 (122·0 to 136·3)	30·7 (27·6 to 34·3)
20 Diabetes	1·1 (1·0 to 1·2)	20 Age-related hearing loss	1·6 (1·2 to 2·1)	82·8 (75·2 to 88·9)	−1·8 (−3·7 to −0·1)
21 Lung cancer	1·0 (1·0 to 1·1)	21 Falls	1·5 (1·4 to 1·7)	47·1 (31·5 to 61·0)	−14·5 (−22·5 to −7·4)
22 Falls	1·0 (0·9 to 1·2)	22 Self-harm	1·3 (1·2 to 1·5)	−5·6 (−14·2 to 3·7)	−38·9 (−44·3 to −33·0)
23 Dietary iron deficiency	1·0 (0·7 to 1·3)	23 Gynaecological diseases	1·2 (0·9 to 1·5)	48·7 (45·8 to 51·8)	−6·8 (−8·7 to −4·9)
24 Interpersonal violence	0·9 (0·9 to 1·0)	24 Anxiety disorders	1·1 (0·8 to 1·5)	53·7 (48·8 to 59·1)	−0·1 (−1·0 to 0·7)
25 Whooping cough	0·9 (0·4 to 1·7)	25 Dietary iron deficiency	1·1 (0·8 to 1·5)	13·8 (10·5 to 17·2)	−16·4 (−18·7 to −14·0)
27 Age-related hearing loss	0·8 (0·6 to 1·1)	26 Interpersonal violence	1·1 (1·0 to 1·2)	10·2 (3·2 to 19·2)	−23·8 (−28·6 to −17·8)
29 Chronic kidney disease	0·8 (0·8 to 0·9)	40 Meningitis	0·6 (0·5 to 0·8)	−51·3 (−59·4 to −42·0)	−57·2 (−64·4 to −48·6)
30 HIV/AIDS	0·8 (0·6 to 1·0)	41 Protein-energy malnutrition	0·6 (0·5 to 0·7)	−71·1 (−79·6 to −59·7)	−74·5 (−82·0 to −64·5)
32 Gynaecological diseases	0·8 (0·6 to 1·0)	46 Drowning	0·5 (0·5 to 0·6)	−60·6 (−65·2 to −53·6)	−68·2 (−71·9 to −62·8)
34 Anxiety disorders	0·7 (0·5 to 1·0)	55 Whooping cough	0·4 (0·2 to 0·7)	−54·5 (−74·6 to −16·9)	−56·3 (−75·6 to −20·3)
35 Other musculoskeletal	0·7 (0·5 to 1·0)	71 Measles	0·3 (0·1 to 0·6)	−89·8 (−92·3 to −86·8)	−90·4 (−92·8 to −87·5)

B 0–9 years

1 Neonatal disorders	23·0 (22·0 to 24·1)	1 Neonatal disorders	32·4 (30·7 to 34·1)	−36·2 (−45·4 to −24·7)	−35·4 (−44·8 to −23·8)
2 Lower respiratory infections	17·0 (14·9 to 19·7)	2 Lower respiratory infections	11·6 (10·5 to 12·6)	−69·1 (−75·9 to −60·9)	−69·6 (−76·3 to −61·6)
3 Diarrhoeal diseases	13·1 (10·7 to 15·1)	3 Diarrhoeal diseases	9·3 (7·9 to 10·8)	−67·8 (−75·3 to −57·2)	−68·5 (−75·9 to −58·4)
4 Congenital birth defects	6·6 (4·6 to 10·0)	4 Congenital birth defects	8·6 (7·4 to 10·7)	−41·6 (−54·6 to −17·4)	−40·1 (−55·1 to −17·9)
5 Measles	5·7 (2·0 to 11·8)	5 Malaria	6·4 (3·3 to 10·8)	−36·9 (−61·4 to −2·2)	−38·5 (−63·1 to −6·5)
6 Malaria	4·6 (2·5 to 7·5)	6 Meningitis	2·1 (1·8 to 2·5)	−59·7 (−68·1 to −49·3)	−61·0 (−69·2 to −51·1)
7 Protein-energy malnutrition	4·1 (3·1 to 5·5)	7 Dietary iron deficiency	2·0 (1·3 to 2·9)	−0·8 (−5·3 to 3·6)	−8·2 (−12·3 to −4·1)
8 Meningitis	2·3 (2·0 to 2·7)	8 Protein-energy malnutrition	2·0 (1·7 to 2·3)	−78·1 (−85·0 to −68·9)	−78·3 (−85·5 to −69·9)
9 Whooping cough	1·9 (0·8 to 3·8)	9 Whooping cough	1·9 (0·9 to 3·3)	−54·7 (−74·7 to −17·3)	−53·2 (−75·6 to −20·4)
10 Drowning	1·8 (1·5 to 2·1)	10 STIs	1·4 (0·5 to 2·8)	−16·3 (−30·7 to 1·7)	−14·9 (−30·1 to 2·5)
11 Tuberculosis	1·8 (1·5 to 2·1)	11 Measles	1·3 (0·4 to 2·7)	−90·0 (−92·6 to −86·9)	−90·5 (−92·9 to −87·6)
12 Tetanus	1·7 (1·4 to 1·9)	12 Road injuries	1·1 (1·0 to 1·4)	−61·5 (−68·7 to −45·0)	−63·7 (−70·8 to −48·8)
13 Road injuries	1·3 (1·1 to 1·5)	13 Tuberculosis	1·0 (0·9 to 1·2)	−74·5 (−79·8 to −67·8)	−75·5 (−80·6 to −69·2)
14 Dietary iron deficiency	0·9 (0·6 to 1·3)	14 HIV/AIDS	1·0 (0·9 to 1·2)	−18·6 (−35·6 to 3·6)	−25·0 (−35·3 to −13·6)
15 STIs	0·7 (0·2 to 1·5)	15 iNTS	1·0 (0·6 to 1·5)	68·3 (27·4 to 121·2)	61·4 (20·6 to 109·3)
16 Typhoid and paratyphoid	0·7 (0·3 to 1·3)	16 Drowning	0·9 (0·8 to 1·1)	−77·6 (−81·3 to −70·1)	−79·0 (−82·6 to −72·2)
17 Foreign body	0·6 (0·5 to 0·7)	17 Haemoglobinopathies	0·9 (0·7 to 1·0)	−10·3 (−30·3 to 22·5)	−13·7 (−34·3 to 14·7)
18 HIV/AIDS	0·6 (0·5 to 0·7)	18 Typhoid and paratyphoid	0·8 (0·4 to 1·5)	−46·7 (−59·1 to −31·1)	−50·7 (−62·5 to −36·9)
19 Encephalitis	0·5 (0·4 to 0·7)	19 Asthma	0·5 (0·4 to 0·8)	−32·2 (−46·2 to −14·5)	−37·5 (−50·0 to −21·5)
20 Acute hepatitis	0·5 (0·4 to 0·5)	20 Foreign body	0·5 (0·4 to 0·5)	−62·9 (−69·6 to −56·2)	−63·6 (−70·2 to −57·1)
21 Haemoglobinopathies	0·4 (0·3 to 0·6)	21 EMBID	0·5 (0·4 to 0·6)	−18·9 (−33·3 to −0·9)	−22·1 (−36·1 to −6·0)
22 Leukaemia	0·4 (0·3 to 0·6)	22 Sudden infant death	0·5 (0·2 to 1·0)	−50·6 (−61·6 to −29·8)	−46·9 (−61·7 to −30·0)
23 Sudden infant death	0·4 (0·2 to 0·9)	23 Idiopathic epilepsy	0·5 (0·3 to 0·6)	−30·7 (−45·8 to 3·6)	−34·0 (−49·1 to −3·8)
24 Asthma	0·4 (0·3 to 0·5)	24 Other unspecified infectious	0·4 (0·3 to 0·6)	−28·4 (−48·3 to 7·8)	−29·3 (−50·3 to 3·3)
25 Falls	0·4 (0·3 to 0·5)	25 Dermatitis	0·4 (0·2 to 0·7)	2·7 (1·7 to 3·7)	−6·0 (−6·9 to −5·1)
28 Idiopathic epilepsy	0·3 (0·2 to 0·4)	26 Leukaemia	0·4 (0·4 to 0·5)	−54·8 (−67·7 to −32·9)	−55·3 (−69·5 to −37·0)
30 Other unspecified infectious	0·3 (0·2 to 0·4)	27 Falls	0·4 (0·3 to 0·5)	−47·2 (−67·0 to −18·0)	−48·3 (−68·7 to −22·6)
33 iNTS	0·3 (0·1 to 0·4)	28 Encephalitis	0·4 (0·3 to 0·5)	−67·6 (−76·7 to −47·6)	−68·5 (−77·9 to −50·2)
34 EMBID	0·3 (0·2 to 0·3)	32 Tetanus	0·3 (0·3 to 0·5)	−91·3 (−93·8 to −85·6)	−91·2 (−93·8 to −85·6)
44 Dermatitis	0·2 (0·1 to 0·3)	39 Acute hepatitis	0·3 (0·2 to 0·3)	−73·1 (−81·7 to −59·1)	−74·1 (−82·6 to −61·1)

Communicable, maternal, neonatal, and nutritional diseases
Non-communicable diseases
Injuries

Figure 2. Leading 25 Level 3 causes of global DALYs and percentage of total DALYs (1990 and 2019), and percentage change in number of DALYs and age-standardised DALY rates from 1990 to 2019 for both sexes combined for all ages (A) ages 50–74 years and (B) and 75 years and older. (Adapted from: GBD 2019. Lancet. 2020)

For further reading please visit https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7567026/

Environmental Risk Factors

TOBACCO

Smoking is the most important risk factor for the development of **COPD**.[1,9] Nicotine is a potent, addictive alkaloid inhaled when smoking tobacco and reaches the nervous system within a few seconds stimulating nicotinic receptors of acetylcholine generating addiction through complex mechanisms. Approximately **15% of smokers develop COPD** so it is clear that there are many other factors that contribute to the presence of the disease. However, multiple studies demonstrate that more than 15% of smokers will develop chronic airway obstruction with **COPD** criteria, with a range of 25%-50%. Second hand smoke, i.e., ambient cigarette smoke inhaled by non-smokers, represents another important risk factor.[9]

Macrophages may be activated by cigarette smoke and other irritants to release neutrophil-chemotactic factors, such as leukotriene B_4 (LTB_4) and interleukin (IL)-8. Neutrophils and macrophages release multiple proteinases that break down connective tissue in the lung parenchyma resulting in emphysema, and stimulate mucus secretion.[9]

Other types of tobacco (e.g., pipe, cigar, water pipe) and marijuana are also risk factors for **COPD**. Passive exposure to cigarette smoke, also known as environmental tobacco smoke (ETS), may also contribute to respiratory symptoms and **COPD**.[1]

OCCUPATIONAL EXPOSURE

Occupational exposures are important causes of **COPD**, contributing to an estimated **14%** of all cases and **31%** of cases among never smokers.[4,10]

Workplace agents associated with COPD include:[10]

- Mineral dusts (coal mine dust, silica, asbestos)
- Organic dusts (cotton, wood, grains)
- Metal/welding fumes (cadmium)
- Diesel/engine exhaust fumes
- Asphalt/tar fumes or vapors in road and roofing operations
- Smoke from fires
- Other chemical gases or vapors

Prevention efforts specific to the industry or agent involved can minimize exposures to these work-related **COPD** agents and prevent the onset of new cases and worsening of existing cases.[10]

In a large UK population-based prospective cohort, De Matteis et al found that six UK Standard Occupational Classification (SOC), v.2000-coded occupations are associated with a significant increase in **COPD** risk:[11,12]

- Sculptor, painter, engraver, art restorer
- Gardener, groundsman, park keeper
- Food, drink and tobacco processor
- Plastics processor, molder
- Agriculture, and fishing occupations not elsewhere classified
- Warehouse stock handler, stacker

These associations were confirmed among **never-smokers** and **never-asthmatics** and, for most, we found supporting positive exposure-response by categories of employment duration.[1]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AND WORK

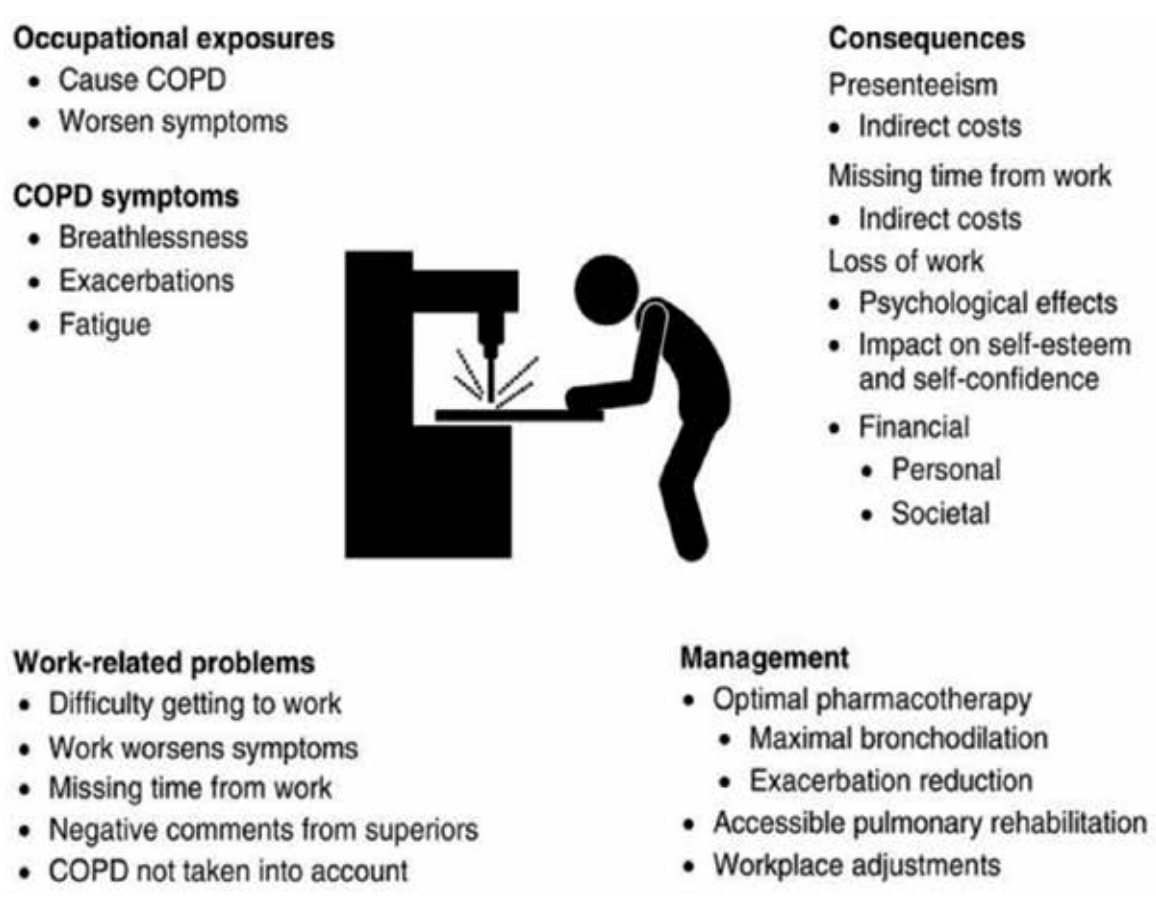


Figure 3. Chronic obstructive pulmonary disease (COPD) and work. (From: Getahun, Biruk, Bekel, Abebe. IntechOpen, 2021).

In addition to causing work to stop, COPD contributes to increased absenteeism. People with COPD are almost half as likely to have a short-term disability and are more than four times more likely to have a long-term disability, but this can also be affected by comorbidity. The efficacy of patients who stay at work can also be limited by symptoms (Figure 3). In the United States and other nations, a number of major cross-sectional studies showed that people with COPD were substantially more likely to report presentism, and findings from studies using self-report data suggest that about 13–18 percent are restricted in what they can do.[13]

For further reading please visit https://www.intechopen.com/chapters/76162

BIOMASS EXPOSURE

While **tobacco smoking remains the leading risk factor** for **COPD** in high income countries, accounting for over **70%** of the cases, in LMICs tobacco smoking contributes to around **30%** to **40%** of the total burden. Because the LMICs together contribute to over 85% of the total burden of **COPD** globally, non-smoking risk factors now contribute to over 50% of the global burden of **COPD**.[1]

Inflammatory cells release high levels of reactive oxygen species (ROS) in **COPD**, which is also found in biomass smoke, and induce oxidative stress *(see Figure 2)*. This process can then activate proteases such as matrix metalloproteinases and neutrophil elastase, and increase inflammatory cell influx at the same time. In turn, these cells will further release more proteolytic enzymes, which can be activated and cause break down of connective tissues in the lung. Therefore, airway inflammation, oxidative stress and protease/antiprotease imbalance are interlinked and all contribute to the development of **COPD**.[14]

There is substantial evidence which links chronic exposure of excess amounts of biomass smoke to adverse health effects notably **COPD**.[13] Further, wood, animal dung, crop residues, and coal, typically burned in open fires or poorly functioning stoves, may lead to very high levels of household air pollution, which is associated with an increased risk of developing **COPD** in LMICs although the extent to which household air pollution versus other poverty-related exposures explain the association is unclear.[1]

Biomass Smoke Exposure

Biomass smoke is one of the major air pollutants and contributors of household air pollution worldwide. It is considered one of the leading environmental risk factors of several diseases, including COPD and acute lower respiratory disease, and is thought to cause 4 million deaths annually across the globe]. Biomass smoke is the result of the combustion of different types of fuels such as wood, animal dung, and crop residues undertaken to create the energy necessary for cooking and heating in many households worldwide. Recent estimates are that 3 billion people rely on biomass fuels for domestic purposes. The proportion of households using biomass fuels varies substantially across the globe (and even in the same continent) due to biomass availability and relative costs compared with other energy sources such as electricity and liquid petroleum gas. This makes quoting percentages per region less informative although there is a clear trend for greater use in the undeveloped and developing world.[14]

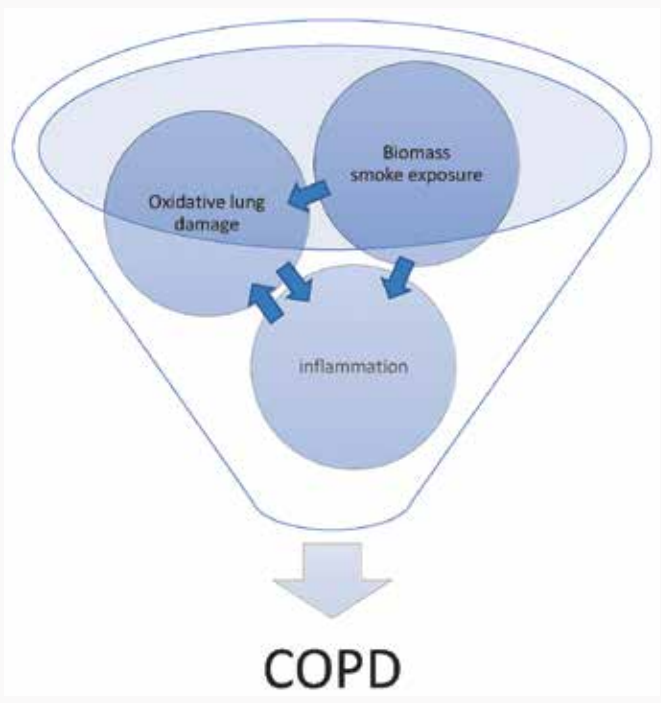


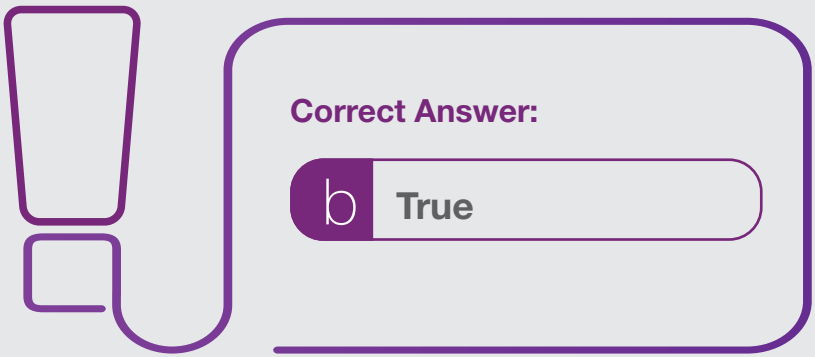
Figure 4. Graphical representation of the interaction of biomass smoke, oxidative lung damage and inflammation in the initiation of chronic obstructive pulmonary disease (COPD). (From: Capistrano SJ, et al. Toxics. 2017).

For further reading, please visit: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5750564/

Besides cigarette smoke, the main risk factors for COPD include socioeconomic factors, genetic factors, gender and respiratory infections in childhood.

a. True

b. False



Correct Answer:

b **True**

Although COPD risk is strongly influenced by cigarette smoking, genetic factors are also important determinants.

While it is very difficult to compare the decline in lung function between men and women because of bias, there is increasing evidence that women are more likely to develop COPD.

Several studies have reported that low socioeconomic status is an important determinant for prevalence and severity of COPD and impaired respiratory health. According to an international survey, socioeconomic disparity is an independent risk factor for COPD, even in countries where healthcare services are free and universal.

Childhood factors such as asthma, maternal smoking, bronchitis, allergic rhinitis, and eczema predisposed children to lung function decline and COPD as adults, according to 2 recent studies.

Sources: 1. Silverman EK. Genetics of COPD. Annu Rev Physiol. 2020 Feb 10;82:413-431. **2.** Curtis JL, Cho MH, Hansel NN. COPD : Pathogenesis and Natural History. In: Murray & Nadel's Textbook of Respiratory Medicine, 63, 850-869.e12. Seventh Edition. Copyright © 2022 by Elsevier, Inc. **3.** Antuni JD, Barnes PJ. Evaluation of individuals at risk for COPD: Beyond the scope of the Global initiative for chronic Obstructive Lung Disease. Chronic Obstr Pulm Dis. 2016; 3(3): 653-667. **4.** Borné Y, Ashraf W, Zaigham S, Frantz S. Socioeconomic circumstances and incidence of chronic obstructive pulmonary disease (COPD) in an urban population in Sweden. COPD. 2019 Feb;16(1):51-57. **5.** Bui DS, Lodge CJ, Burgess JA, Lowe AJ, Perret J, Bui MQ, Bowatte G, Gurrin L, Johns DP, Thompson BR, Hamilton GS, Frith PA, James AL, Thomas PS, Jarvis D, Svanes C, Russell M, Morrison SC, Feather I, Allen KJ, Wood-Baker R, Hopper J, Giles GG, Abramson MJ, Walters EH, Matheson MC, Dharmage SC. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. Lancet Respir Med. 2018 Jul;6(7):535-544.

Predisposing Factors

GENETIC RISKS

Although chronic obstructive pulmonary disease (COPD) risk is strongly influenced by cigarette smoking, genetic factors are also important determinants of COPD. In addition to Mendelian syndromes such as alpha-1 antitrypsin deficiency, many genomic regions that influence COPD susceptibility have been identified in genome-wide association studies. Similarly, multiple genomic regions associated with COPD-related phenotypes, such as quantitative emphysema measures, have been found. Identifying the functional variants and key genes within these association regions remains a major challenge. However, newly identified COPD susceptibility genes are already providing novel insights into COPD pathogenesis. Network-based approaches that leverage these genetic discoveries have the potential to assist in decoding the complex genetic architecture of COPD.[15]

GENDER

While it is very difficult to compare the decline in lung function between men and women because of bias, there is increasing evidence that women are more likely to develop COPD.[4,9]

SOCIOECONOMIC STATUS

In the setting of COPD, socioeconomic status (SES) has an inverse relationship with COPD prevalence, mortality, health utilization costs and health related quality of life (HRQoL).[16] Several studies have reported that low SES is an important determinant for prevalence and severity of COPD and impaired respiratory health. According to an international survey, socioeconomic disparity is an independent risk factor for COPD even in countries where healthcare services are free and universal.[17]

Childhood Disadvantage Factors

COPD can start early in life and take a long time to manifest clinically. Identifying "early" COPD is difficult.[1] Childhood factors such as asthma, maternal smoking, bronchitis, allergic rhinitis, and eczema predisposed children to lung function decline and COPD as adults, according to 2 recent studies. Risks might be minimized by reducing maternal smoking, encouraging immunizations, having good asthma control, and avoiding smoking.[18]

One study was unique because it was the first to track lung function from childhood to the sixth decade in a large population sample.[17] Researchers followed 8583 participants in the Tasmanian Longitudinal Health Study and investigated mean forced expiratory volume in 1 second (FEV_1) trajectories from age 7 to age 53. Lung function measurements were taken at ages 7, 13, 18, 45, 50, and 53.[18]

By adulthood, most COPD cases were clustered in participants whose FEV_1 fell into these categories: early below average, accelerated decline FEV_1, below average FEV_1, and persistently low FEV_1.

Predictors of these 3 trajectories included childhood asthma, bronchitis, pneumonia, allergic rhinitis, eczema, parental asthma, and maternal smoking. There were borderline associations with food allergy and childhood underweight. Additionally, asthma in combination with either eczema or allergic rhinitis had a multiplicative effect.[18]

The researchers said their findings contradict beliefs that lung function established in childhood tracks throughout life.[18]

Maternal smoking adversely affects not only early lung function, but predisposes children to more rapid lung function decline if they, too, take up smoking. In addition, the researchers said their findings highlight the potential role of lifelong asthma control in promoting lung health and preventing COPD.[18]

In another study, researchers studied trajectories of FEV_1 in 2 birth cohorts with repeat spirometry from 5 years to 24 years. One group had 1046 participants aged 5 to 16 years and another group was made up of 1,390 participants aged 8 to 24.[19]

A third, smaller group was followed with repeat lung function measures from infancy and follow-up until age 18.[19]

Of 4 FEV_1 trajectories, one (the persistently low trajectory) was marked by low FEV_1 from school age to adulthood. Factors associated with this group included recurrent wheeze with severe wheezing exacerbations, early allergic sensitization, and tobacco smoke exposure.[19]

Definition of Early COPD, Pre-COPD and Overt COPD

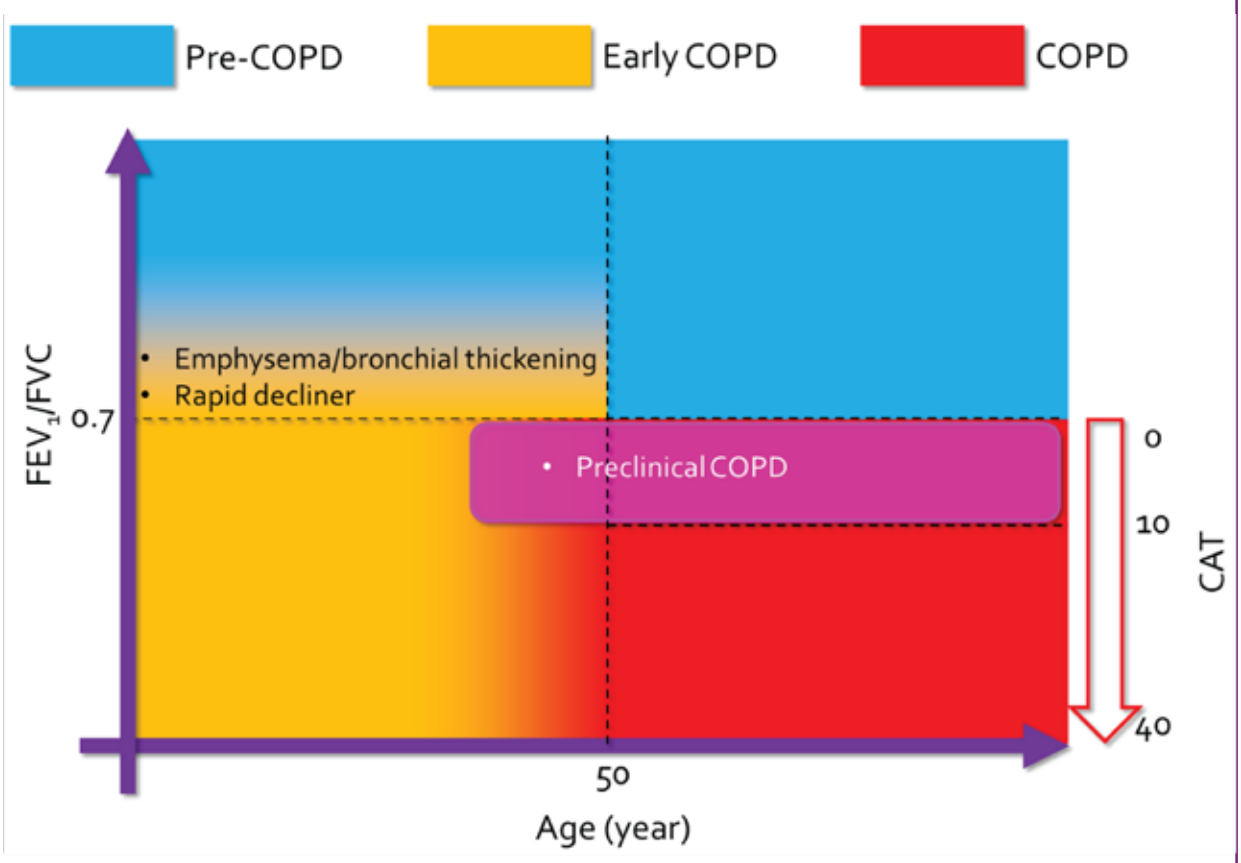


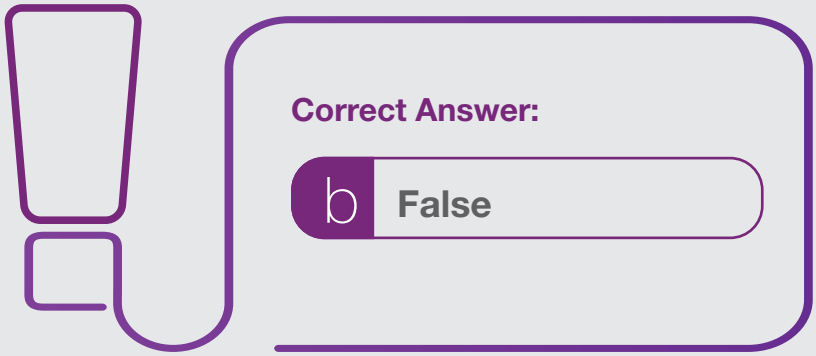
Figure 5. Definition of early COPD, pre-COPD and overt COPD. (From: Choi JY, et al. J Clin Med. 2020).
In 2020, Martinez et al proposed a definition of early COPD in which diagnosis is made in patients <50 years of age with a smoking history ≥ 10 pack-years and fulfilling one or more of the following: FEV1/forced vital capacity (FVC) below the lower normal limit; compatible computed tomography (CT) abnormalities, such as visual emphysema, air trapping, or bronchial thickening; evidence of accelerated FEV1 decline (≥60 mL/year). This definition was established based on operational and practical considerations assuming that patients at an early age may not have developed significant COPD.[20]

For further reading please visit: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7692717

Airway hyperresponsiveness, childhood asthma, environmental, recurrent bronchopulmonary infections and chronic mucus hypersecretion are all risk factors for COPD development, but the most important risk factor, only second to smoking is emphysema.

a. True

b. False



After smoking, airway hyperresponsiveness is the most important risk factor for COPD, which is responsible for 15–17% of new cases in young adults.

A self-reported history of childhood asthma is a valid method for defining a population that phenotypically and genetically represent asthmatic subjects among a cohort of adult smokers at risk for COPD.

Chronic airway mucus hypersecretion can cause progressive decline in pulmonary function among COPD patients.

Some individuals develop changes in the lung structure with an increase in the size of the alveolar spaces (over-distension) without inflammation or alveolar wall destruction, so-called “senile emphysema” a term that has been discarded. By contrast, some individuals mostly smokers may develop “real” emphysema characterized by alterations of the extracellular matrix, destruction of the alveolar walls and loss of the lung architecture. These changes are usually, but not always associated with airways alterations constituting COPD.

Sources: 1. Choi JY, Rhee CK. Diagnosis and Treatment of Early Chronic Obstructive Lung Disease (COPD). J Clin Med. 2020 Oct 26;9(11):3426. doi: 10.3390/jcm9113426. **2.** Hayden LP, Cho MH, Raby BA, Beaty TH, Silverman EK, Hersh CP; COPDGene Investigators. Childhood asthma is associated with COPD and known asthma variants in COPDGene: a genome-wide association study. Respir Res. 2018 Oct 29;19(1):209. **3.** Tian PW, Wen FQ. Clinical significance of airway mucus hypersecretion in chronic obstructive pulmonary disease. J Transl Int Med. 2015 Jun-Sep;3(3):89-92. **4.** Buendia-Roldan I, Palma-Lopez A, Chan-Padilla D, Herrera I, Maldonado M, Fernández R, Martínez-Briseño D, Mejia M, Selman M. Risk factors associated with the detection of pulmonary emphysema in older asymptomatic respiratory subjects. BMC Pulm Med. 2020 Jun 9;20(1):164.

Lung Conditions

AIRWAY HYPERRESPONSIVENESS

After smoking, airway hyperresponsiveness is the most important risk factor for COPD, which is responsible for 15–17% of new cases in young adults. Patients with a history of asthma who develop COPD in later years may be categorized as asthma–COPD overlap (ACO) according to the American Thoracic Society (ATS) roundtable criteria and modified Spanish COPD guidelines.[20]

ASTHMA

A self-reported history of childhood asthma is a valid method for defining a population that phenotypically and genetically represent asthmatic subjects among a cohort of adult smokers at risk for COPD.[21]

Asthma and chronic obstructive pulmonary disease (COPD) are common chronic respiratory diseases in the general population. Distinguishing between these conditions can be problematic, especially among older adults. In fact, some patients with asthma, in particular smokers, develop fixed airflow obstruction and COPD at older ages. Some patients with COPD show clinical features that are commonly observed in asthma, such as airway hyperresponsiveness (AHR), bronchodilator responsiveness (BDR) and increased eosinophils in blood and airways, although the development of asthma is less common among these patients.[22]

CHRONIC MUCUS HYPERSECRETION

Chronic airway mucus hypersecretion can cause progressive decline in pulmonary function among COPD patients. A 12-year follow-up study of 1,757 males and 2,191 females revealed the relation between chronic phlegm and FEV_1 decline after adjustment for age and cigarette smoking. In the study, men and women with chronic phlegm show FEV_1 decline of (4.5±2.0) ml/yr and (1.7±1.5) ml/year, respectively. Further, a 5-year follow-up study on 5,354 women and 4,081 men found that chronic airway mucus hypersecretion was significantly associated with FEV_1 decline among COPD patients. The study showed that chronic airway mucus hypersecretion is associated with an excess FEV_1 decline of 22.8 ml/year, compared with men without airway mucus hypersecretion after adjusting for age, height, weight, and smoking; in women, the excess decline was 12.6 ml/year.[23]

Chronic cough and phlegm significantly increase death risk. In a clinical study, 1,711 middle-aged men were followed up for up to 40 years; the statistical analysis shows that persistent cough and phlegm increased death risk related to respiratory disorders by 2.54 times and total death risk by 1.64 times after adjusting for lung function.[23]

RECURRENT BRONCHOPULMONARY INFECTIONS

Lower respiratory tract infections (LRTIs) are important to consider when thinking about a diagnosis of COPD. Following the National Institute for Health and Care Excellence (NICE) COPD guidelines, a diagnosis should be suspected in people who experience frequent winter bronchitis (ie, multiple LRTIs) or present with symptoms such as breathlessness, chronic cough, sputum production or wheeze. It is therefore possible that individuals may have several LRTI events prior to COPD diagnosis. The frequency and severity of LRTI events prior to first COPD diagnosis are associated with future increased rates of exacerbations of COPD, all-cause mortality and COPD-related mortality.[24]

EMPHYSEMA

Aging is a normal biological process associated with multiple anatomic and functional abnormalities and morbidities. The physiological effects of aging in the lungs include, among others, a progressive decrease in forced vital capacity with an increase of pulmonary vascular resistance. The lungs of older people may also show interstitial lung abnormalities, decreased elastic recoil and decreased diameter of the small airways with the premature close of the peripheral airways[25]

Some individuals develop changes in the lung structure with an increase in the size of the alveolar spaces (over-distension) without inflammation or alveolar wall destruction, so-called "senile emphysema" a term that has been discarded. By contrast, some individuals mostly smokers may develop "real" emphysema characterized by alterations of the extracellular matrix, destruction of the alveolar walls and loss of the lung architecture. These changes are usually, but not always associated with airways alterations constituting COPD.[25]

Risk factors associated with the detection of pulmonary emphysema in older asymptomatic respiratory subjects[25]

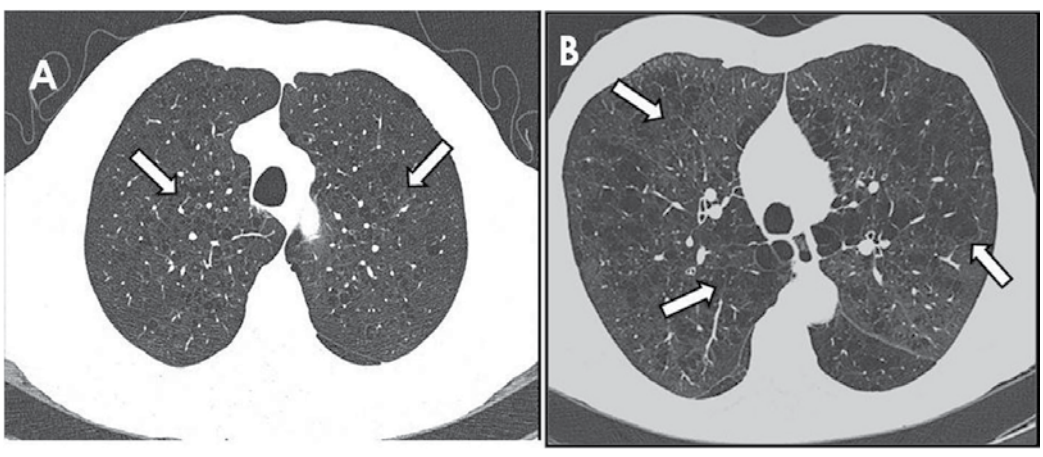


Figure 6. a and b show high resolution computed tomography of two different respiratory asymptomatic individuals with different severity of emphysematous lesions (arrows) (From: Buendia-Roldan I, et al. BMC Pulm Med. 2020).

Pulmonary emphysema represents a form of destruction of the lung architecture characterized by an abnormal and permanent enlargement of the air space distal to the terminal bronchioles, with the destruction of the alveolar walls, and without obvious fibrosis.[25] Emphysema, usually as part of COPD, represents a slowly progressive and irreversible lung disorder, resulting in respiratory insufficiency and reduction in life expectancy and life quality. Pulmonary emphysema may occur associated with gene mutations such as alpha1-antitrypsin and telomerase components, but the sporadic form associated with COPD, is primarily related with the exposure to cigarette smoke and other respiratory environmental or occupational exposures such as gases, biomass smoke, fumes and dust.[25]

For further reading please visit:
https://bmcpulmmed.biomedcentral.com/articles/10.1186/s12890-020-01204-9

LUNG GROWTH, AGEING, AND LUNG FUNCTION DECLINE

The lungs grow progressively up to the age of 25 with a plateau until about the age of 35-40, then starting an ageing process with a gradual decline of FEV_1. The estimated average decline in FEV_1 is 30 ml/year in men and 23 ml/year in women although there is considerable inter-individual variability.[9]

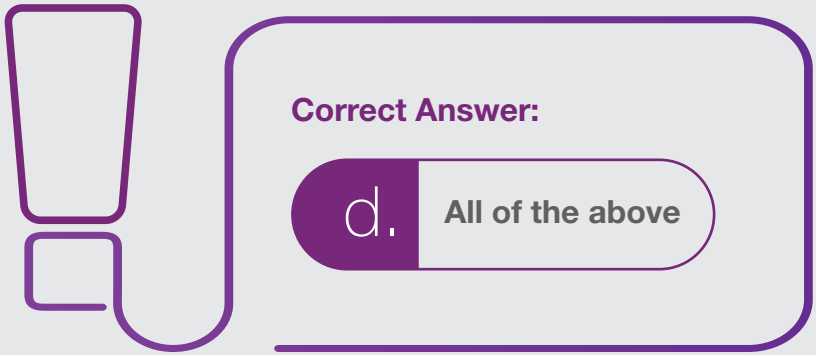
Which of the below statements is correct?

a. In patients with COPD pathological changes can be found in the airways, lung parenchyma, and pulmonary vasculature

b. COPD is an inflammatory lung disease, caused by an imbalance between pro-inflammatory cytokines, enzymes, and effector cells, and the pulmonary defense mechanisms

c. The number of pro-inflammatory cells, including circulating neutrophils and CD8 T lymphocytes as well as the number of macrophages in bronchial mucosa is increased in COPD

d. All of the above



In patients with COPD pathological changes can be found in the airways, lung parenchyma, and pulmonary vasculature.

COPD is an inflammatory lung disease, caused by an imbalance between pro-inflammatory cytokines, enzymes, and effector cells, and the pulmonary defense mechanisms. An increase is seen in the number of pro-inflammatory cells, including circulating neutrophils and CD8 T lymphocytes as well as the number of macrophages in bronchial mucosa.

Sources: 1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2023 Report). © 2022, 2023 Global Initiative for Chronic Obstructive Lung Disease, Inc. Available at https://goldcopd.org/wp-content/uploads/2022/12/GOLD-2023-ver-1.1-2Dec2022_WMV.pdf Accessed January 2, 2023. **2.** Timbadia PJ, Fagan JB. Chronic Obstructive Pulmonary Disease. In: Kellerman RD and Rakel DP (Eds) Conn's Current Therapy 2023, 897-902 Copyright © 2023 by Elsevier, Inc. All rights reserved.

Pathophysiology of COPD

In patients with COPD pathological changes can be found in the airways, lung parenchyma, and pulmonary vasculature. These include inflammatory and structural changes which increase with the severity of airflow obstruction and can persist on smoking cessation.[1]

COPD is an **inflammatory lung disease, caused by an imbalance between pro-inflammatory cytokines, enzymes, and effector cells, and the pulmonary defense mechanisms**. An increase is seen in the number of pro-inflammatory cells, including circulating neutrophils and CD8 T lymphocytes as well as the number of macrophages in bronchial mucosa. $CD8^+$ cells have the potential to release tumor necrosis factor α, perforins, and granzymes, though the exact role of T lymphocytes in COPD remains unclear. Neutrophils produce proteases which have the potential to cause alveolar destruction, elastase destruction, and mucus hypersecretion. Macrophages produce proteases as well as a variety of inflammatory mediators. Cigarette smoke promotes the release of these pro-inflammatory mediators and also inactivates several anti-proteases, causing an inflammation/antiinflammation imbalance. This imbalance causes a cycle of injury and repair which results in permanent damage to airways, lung parenchyma, and vasculature. The airways become narrowed by increased numbers of goblet cells, increased size of submucosal glands, mucosal thickening, collagen deposition, ciliary dysfunction (promoting retention of secretions within the airway), and destruction of alveolar walls and alveolar support. Loss of pulmonary vascular bed, vascular remodeling, and arterial vasoconstriction lead to hypoxemia from ventilation perfusion mismatch and pulmonary hypertension.[26]

The **inflammatory response and obstruction of the airways cause a decrease in the forced expiratory volume (FEV1) and tissue destruction leads to airflow limitation and impaired gas exchange**. Hyperinflation of the lungs is often seen on imaging studies and occurs due to air trapping from airway collapse during exhalation. The inability to fully exhale also causes elevations in carbon dioxide (CO2) levels. As the disease progresses, impairment of gas exchange is often seen. The reduction in ventilation or increase in physiologic dead space leads to CO2 retention. Pulmonary hypertension may occur due to diffuse vasoconstriction from hypoxemia.[27]

COPD Pathophysiology

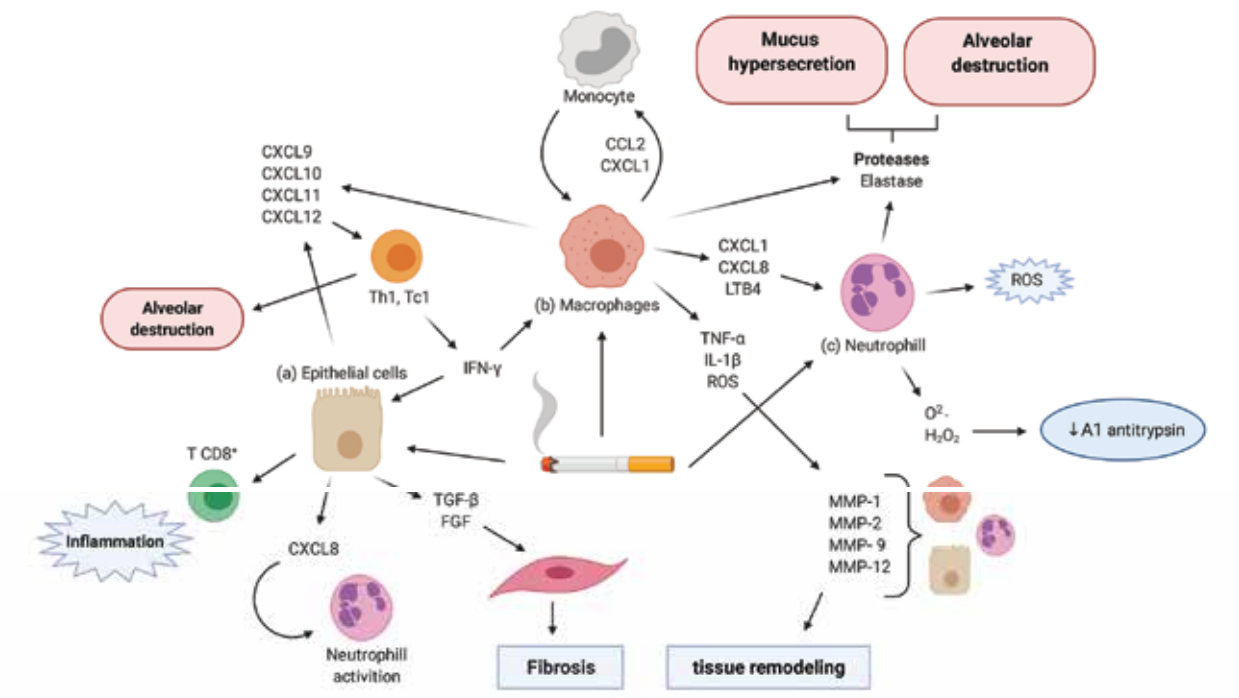


Figure 7. COPD Pathophysiology. The toxins present in cigarette smoke lead to the recruitment of inflammatory cells and the release of inflammatory mediators. Macrophages release CXCL1, CXCL8, and LTB4, which attract neutrophils, and CCL2 and CXCL1, which attract monocytes. Neutrophils release ROS, enhancing inflammation and reductively inactivating α1 antitrypsin. They also release proteases, such as NE, leading to tissue damage. Epithelial cells and macrophages release CXCL9, CXCL10, CXCL11, and CXCL12, which attract Th1 and Tc1 lymphocytes. They also release IFN-γ, leading to alveolar destruction. Epithelial cells release CXCL8, recruiting and activating neutrophils, and TGF-β and FGF, recruiting fibroblasts that promote tissue fibrosis. Epithelial cells also attract CD8+ T cells believed to foster inflammation. Macrophages release TNF-α, IL-1β, and ROS, inducing MMP secretion by epithelial cells, macrophages, and neutrophils, causing tissue remodeling. CXCL1, chemokine (C-X-C motif) ligand 1; LTB4, leukotriene B4; CC, Chemokine (C-C motif); IFNγ, interferon gamma; TGF, transforming growth factor; FGF, fibroblast growth factor; TNF-α, tumor necrosis factor alpha; IL, interleukins; ROS, reactive oxygen species; MMPs, metalloproteinases. (From: Rodrigues SO, et al. Pharmaceuticals (Basel). 2021).

For further reading, please visit https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8539950/

Most patients with COPD present to their provider with **complaints of dyspnea, cough, and sputum production, or decreased activity capacity**. This presentation may be relatively late in the disease course. Many smokers accept their cough as a "smoker's cough." Non-smokers have a large ventilatory reserve: although inhalation is about 5 L/min, the maximum ventilatory volume is approximately 180 L/min. Because of this, especially if the patient is sedentary, they may not notice dyspnea until there has been considerable loss of pulmonary function.[26]

Spirometry is the cornerstone of diagnosis of COPD.[1,26] However, despite its good sensitivity, peak expiratory flow measurement alone cannot be reliably used as the only diagnostic test because of its weak specificity.[1] Airway obstruction is defined by a forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) of <70%. Patients with airway obstruction may be able to exhale much of their vital capacity (VC), but because of airways narrowing, they cannot do it very quickly, resulting in the low ratio. The degree of obstruction is defined by the FEV 1 percent of predicted value. It is recommended that an A1A be obtained in all patients diagnosed with COPD. It is important to note that A1A is an acute-phase reactant and can be elevated during an exacerbation of COPD; it is therefore best to obtain when the patient is clinically stable.[26]

GOLD Grades and Severity of airway obstruction in COPD

(based on post-bronchodilator FEV_1)[1]

In COPD patients (FEV_1/FVC < 0.7):

- **GOLD 1: Mild** — FEV_1 ≥80% predicted
- **GOLD 2: Moderate** — 5O% ≤ FEV_1 < 80% predicted
- **GOLD 3: Severe** — 30%≤ FEV_1 < 50% predicted
- **GOLD 4: Very severe** — FEV_1 < 30% predicted

When measuring breathlessness, which is a key symptom in many patients with COPD, although often unrecognized, the Modified Medical Research Council Dyspnea Scale (mMRC) should be adopted as the classification criterion for symptom assessment in the GOLD ABCD system when focusing on physical activities of daily living (PADL). The mMRC scale was the first questionnaire developed to measure breathlessness while the most comprehensive disease-specific health status questionnaires such as the Chronic Respiratory Questionnaire (CRQ)(89) and St. George's Respiratory Questionnaire (SGRQ)(90) are important research tools but they are too complex to use in routine practice. Shorter comprehensive measures, such as the COPD Assessment Test (CAT™) and The COPD Control Questionnaire (CCQ©) have been developed and are suitable for use in the clinic.[1]

Diagnostic Criteria

- In the appropriate clinical context, the presence of non-fully reversible airflow limitation (i.e., FEV_1/FVC < 0.7 post-bronchodilation) measured by spirometry confirms the diagnosis of COPD[1]
- Among the updates in the 2023 GOLD Report, the section on diagnostic criteria added a proposed new category "PRISm," denoting "preserved ratio impaired spirometry," encompassing individuals who present with structural lung lesions (for example, emphysema) and/or other physiological abnormalities such as low-normal forced expiratory volume in 1 second (FEV1), gas trapping, hyperinflation, reduced lung diffusing capacity and/or rapid FEV1 decline, but without airflow obstruction (FEV_1/FEV ≥ 0.7 post bronchodilation). Some of these "pre-COPD" (chronic obstructive pulmonary disease) individuals, who have a normal ratio but abnormal spirometry are at risk over time of developing airflow obstruction. The best treatment for them, beyond smoking cessation, needs to be determined through research[1]

The Modified Medical Research Council (mMRC) Scale

Grade	Description of breathlessness
Grade 0	I only get breathless with strenuous exercise
Grade 1	I get short of breath when hurrying on level ground or walking up a slight hill
Grade 2	On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level
Grade 3	I stop for breath after walking about 100 yards or after a few minutes on level ground
Grade 4	I am too breathless to leave the house or I am breathless when dressing

(From: Launois C, Barbe C, Bertin E, Nardi J, Perotin JM, Dury S, Lebargy F, Deslee G. The modified Medical Research Council scale for the assessment of dyspnea in daily living in obesity: a pilot study. BMC Pulm Med. 2012 Oct 1;12:61.)

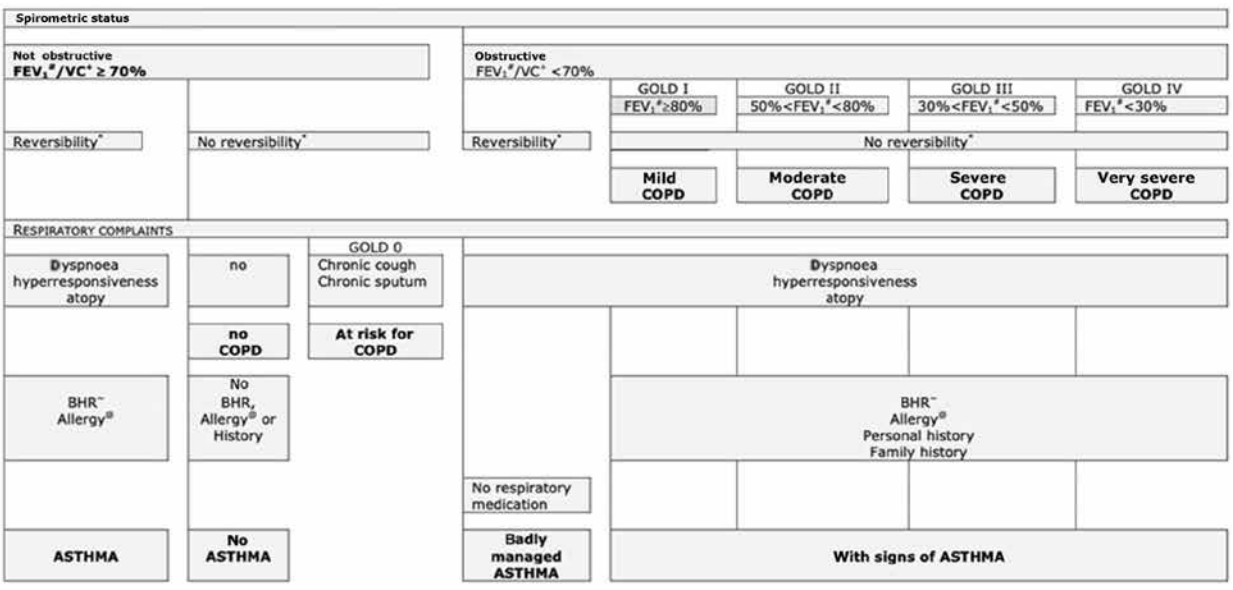
The **COPD Assessment Test** (CAT) is a **validated, disease-specific, patient-completed questionnaire** that is simple and quick to perform. It comprises 8 items which assess: cough, phlegm, chest tightness, breathlessness when going uphill or upstairs, any activity limitation at home, confidence leaving home, sleep, and energy. Each item is scored 0–5 to provide an overall total score of 0–40. Higher CAT scores indicate increased disease burden and worse health status. The CAT score has also been incorporated into the GOLD strategy document to help guide initial pharmacological treatment of COPD.[29] A CAT score ≥10 denotes symptomatic COPD and is predictive of exacerbation risk.[29]

COPD may be confused with other obstructive airway diseases, most notably asthma. Asthma will most often present at a younger age, though it may be diagnosed during any decade of life. Asthmatics generally have more reversibility and less fixed obstruction, but overlap is seen. Both may have hyperinflation and reduction in forced expiratory flows on pulmonary function testing, but a reduction in diffusing capacity would be more characteristic of **COPD**.[26]

Diagnostic differentiation between asthma and COPD in primary care using lung function testing

Asthma and COPD are defined as different disease entities, but in practice patients often show features of both diseases making it challenging for primary care clinicians to establish a correct diagnosis.[30]

Asthma and COPD are both common chronic respiratory diseases affecting approximately 1 in 12 people worldwide. The two conditions are defined as different disease entities with unique pathophysiological mechanisms and characteristic clinical features. The underlying pathophysiology in COPD is characterized predominantly by neutrophilic inflammation, whereas in asthma the inflammatory pattern is mostly due to eosinophilic inflammation. Asthma typically presents with intermittent respiratory symptoms caused by airflow obstruction predominantly due to bronchial hyperresponsiveness. Asthma is often presented at younger age as part of an atopic constitution, but can also be diagnosed in adulthood. In contrast, COPD is a slowly progressive lung disease with patients having persistent respiratory symptoms and airflow obstruction.[2]



#Postbronchodilator forced expiratory volume. +Postbronchodilator vital capacity. *12% change in FEV1 (after bronchodilation), with a change of at least 200 mL. ~ Bronchial hyperresponsiveness (positive at a provocative histamine concentration ≤8mg/mL). @Skin prick test.

Figure 8. Decision tree used by the chest physicians to support their assessment of chronic lung disease diagnoses based on GOLD and GINA guidelines. (From: Bouwens JDM, et al. NPJ Prim Care Respir Med. 2022).

For further reading please visit https://www.nature.com/articles/s41533-022-00298-4

Asthma–COPD Overlap (ACO)

Although **COPD and asthma** are well-characterized diseases, they can coexist in a given patient. The term asthma–COPD overlap (ACO) was introduced to describe patients that have clinical features of both diseases and may represent around 25% of COPD patients and around 20% of asthma patients.[31]

Schematic approach for investigating and diagnosing asthma and COPD overlap

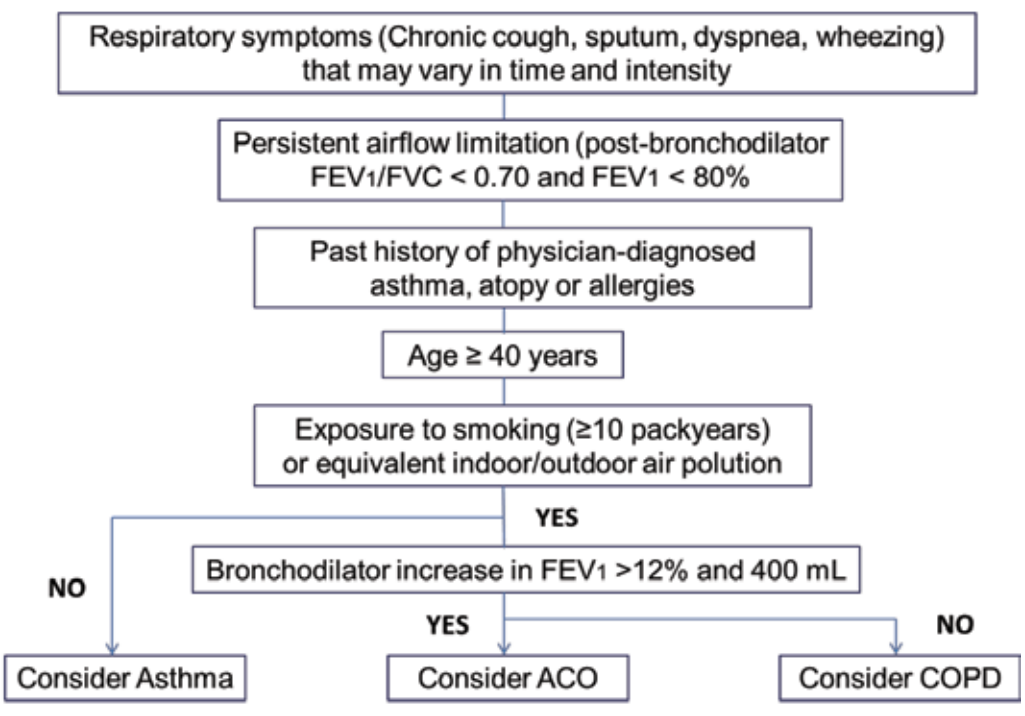
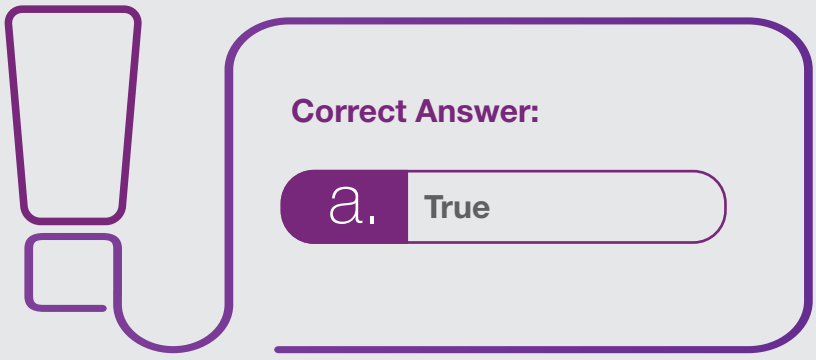


Figure 9. Flow-chart for diagnosing asthma-COPD overlap. ACO: asthma COPD overlap; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; FVC: forced vital capacity. (From: Fouka E, et al. J Pers Med. 2022).

According to the latest GOLD 2023 Report, a bronchodilator is recommended for GOLD group A patients with 0 or 1 moderate exacerbations that do not lead to hospital admission.

a. True

b. False



The GOLD 2023 Report also offers proposed clinical guidance, in the absence of high-quality clinical trial evidence, on initial pharmacologic management of COPD. The proposal is based on individual assessment of symptoms and exacerbation risk following use of the ABE Assessment Tool, a revised version of the ABCD Assessment Tool that recognizes the clinical relevance of exacerbations independent of symptom level.

These updates to information and figures pertaining to initial pharmacological treatment and follow-up pharmacological treatment revise the positioning of LABA (long-acting beta2 agonists) plus LAMA (long-acting muscarinic agonists) and LABA/ICS (inhaled corticosteroids). Among GOLD group A patients with 0 or 1 moderate exacerbations that do not lead to hospital admission, a bronchodilator is recommended.

Source: Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2023 Report). © 2022, 2023 Global Initiative for Chronic Obstructive Lung Disease, Inc. Available at https://goldcopd.org/wp-content/uploads/2022/12/GOLD-2023-ver-1.1-2Dec2022_WMV.pdf Accessed January 2, 2023

Treatment of COPD

The GOLD 2023 Report offers proposed clinical guidance, in the absence of high-quality clinical trial evidence, on initial pharmacologic management of COPD. The proposal is based on individual assessment of symptoms and exacerbation risk following use of the ABE Assessment Tool, a revised version of the ABCD Assessment Tool that recognizes the clinical relevance of exacerbations independent of symptom level.[1]

These updates to information and figures pertaining to initial pharmacological treatment and follow-up pharmacological treatment revise the positioning of LABA (long-acting beta$_2$ agonists) plus LAMA (long-acting muscarinic agonists) and LABA/ICS (inhaled corticosteroids). Among GOLD group A patients with 0 or 1 moderate exacerbations that do not lead to hospital admission, a bronchodilator is recommended.[1]

The recommendation for group B patients is LABA/LAMA with the caveat that single inhaler therapy may be more convenient and effective than multiple inhalers. For group E patients with two or more moderate exacerbations or one or more leading to hospitalization, LABA/LAMA is recommended (with the same inhaler therapy caveat). With blood eosinophil levels at 300 cells/μL or higher, LABA/LAMA/ICS may be considered.[1] There is high quality evidence from randomized controlled trials (RCTs) that ICS use modifies the airway microbiome and is associated with higher prevalence of oral candidiasis, hoarse voice, skin bruising and pneumonia.[1]

Non-pharmacological Treatment

SMOKING CESSATION

Tobacco smoking is the leading cause of preventable death in the western world. The overall mortality for people who smoke is three times higher than for people who have never smoked. COPD can be treated through pharmacological and non-pharmacological interventions. The most effective way to inhibit disease progression is smoking cessation. Smoking cessation in patients with COPD is associated with decreased dyspnea, fewer exacerbations and hospitalizations, better lung function, increased quality of life, and increased survival.[32]

For further study please visit https://www.nature.com/articles/s41533-022-00301-y

PHARMACOTHERAPY and NON-PHARMACOTHERAPY for the smoking cessation

Nicotine replacement therapies such as nicotine gum, inhaler, transdermal patch, lozenge, sublingual tablet and nasal spray can increase smoking cessation success rates compared with placebo. The contraindications to nicotine replacement therapy are recent myocardial ischemia or stroke. Although controversial, it is suggested that after an acute coronary syndrome, nicotine replacement be started 2 weeks or later from the event onset.[36,34]

E-cigarettes as smoking cessation agents are controversial despite their increasing use in this setting. Evidence shows that e-cigarettes can have detrimental effects on several cell lines and animal models with their flavorings and nicotine content implicated; this has, however, not translated into major health outcomes after 3.5 years follow-up but has been linked to chronic lung disease and cardiovascular disease. While advertised as an effective smoking cessation tool, no consensus can be made regarding their effectiveness although the first robust randomized controlled trial reports some success. This, however, is offset by the fact that the most common e-cigarette use is as a dual user and that there is evidence of threefold increased risk of future tobacco smoking.[35]

A systematic review evaluated the efficacy and safety of e-cigarettes in helping people who smoke to achieve abstinence at 24–26 and 52 weeks, compared with electronic non-nicotine delivery systems (ENNDS, no nicotine), or any comparator recommended for smoking cessation treatment or combination of treatments using RCTs. The researchers concluded that there is no clear evidence of a difference in effect between nicotine containing e-cigarettes and nicotine replacement therapy (NRT) on incidences of smoking cessation at 24–26 weeks, and substantial uncertainty remains.[36]

A network meta-analysis based on randomized controlled trials investigating the effects of pharmacological interventions on smoking cessation included a total of 159 studies involving 60,285 smokers.[37] The analysis involved 15 interventions and which yielded 105 pairs of comparisons, which showed that most pharmacological interventions demonstrated a benefit in smoking cessation compared with placebo, whether monotherapy or combination therapy. Among all monotherapies, varenicline showed a higher level of evidence of smoking cessation. Furthermore, confirmed evidence suggested that some combination treatments, such as varenicline plus bupropion and nicotine replacement therapy plus mecamylamine have a higher probability of being the best smoking cessation interventions.[36]

VACCINATIONS

The **GOLD recommends influenza vaccination** at evidence A level due to its ability to reduce hospitalization and mortality rates, and pneumococcal vaccination at evidence B level to prevent community-acquired pneumonia. In this case, the long-term consequences of any of these infections, in particular in elderly patients, may be very serious, up to disability and an increased risk of death. Vaccines of two types are currently used to prevent pneumococcal infections: 13-valent conjugate vaccine and 23-valent polysaccharide vaccine. Conjugate vaccines proved to have a prolonged effect and persistent clinical effectiveness in all age groups. It was demonstrated for COPD patients that PPV23 significantly reduces the pneumonia incidence rate over a 3-year period in COPD patients younger than 65 years, in patients with severe respiratory disturbance (predicted FEV_1 <40%), and those having cardiovascular comorbidities. However, only the overall effectiveness in reducing the risks of developing pneumonia in elderly patients (above 65 years) and COPD patients has been demonstrated for PCV13.[38]

For further study, please visit https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8342495/

COPD and COVID vaccination

A **study which tested the immune response of COPD patients to COVID-19 vaccination** has shown they respond in a similar way to healthy people. The scientists compared the SARS-COV-2 vaccine- specific immune responses in COPD patients with healthy people, using blood, nasal and airway samples. Vaccinated individuals, who had never been infected with COVID-19, donated samples more than two weeks after completing two doses of either the Oxford-AstraZeneca or Pfizer vaccine. Samples were analyzed from 27 vaccinated individuals: 11 with COPD and 16 healthy; and 43 pre-vaccinated individuals: 24 with COPD and 19 healthy. Both vaccinated COPD patients and healthy individuals had higher anti-spike protein IgG antibody levels in plasma and airways compared to unvaccinated COPD patients and healthy individuals, with the level of vaccine-induced responses being similar in COPD patients and healthy subjects. The 2023 GOLD Report recommends that "COVID-19 vaccines are highly effective against SARS-CoV-2 infection and people with COPD should have the COVID-19 vaccination in line with national recommendations."[1]

Physical activity

Physical activity (PA) is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. Types of PA in daily life can be categorized into occupational sports, transportation (e.g., cycling and walking), household (e.g., yard work cleaning and home maintenance) or other activities. Strong evidence demonstrates regular PA is beneficial to reducing the risk of many chronic diseases.[40]

The **GOLD guidelines recommend regular physical activity for all patients with COPD, which significantly improves dyspnea, health status, and exercise tolerance.**[1,37] Equally, both the ATS/ European Respiratory Society (ERS) note that PA can significantly improve health outcomes in people with COPD. For example, a study found that **COPD patients with high levels of physical activity had a 34% lower risk of 30-day readmission and a 47% lower risk of death within 12 months of discharge compared** to inactive patients.[39]

For further study, please visit https://bmcpulmmed.biomedcentral.com/articles/10.1186/s12890-022-02099-4

According to the latest 2023 GOLD report, initial pharmacological treatment is based on individual assessment of symptoms and exacerbation risk following use of the Achieving Best Evidence (ABE) Assessment Tool, a revised version of the ABCD Assessment Tool that recognizes the clinical relevance of exacerbations independent of symptom level.

a. **GOLD recommends long-acting muscarinic antagonist (LAMA)/long-acting beta-agonist (LABA) combination therapy for most patients (Groups B and E) as initial therapy, with bronchodilators recommended for patients in Group A.**

b. **The combination of LABA and an inhaled corticosteroid (ICS) is no longer recommended in Group B**

c. **The combination of LABA and an inhaled corticosteroid (ICS) is only recommended to be considered in Group E it if blood eosinophils are ≥ 300 cells/µL**

d. **All of the above**

Correct Answer:

d. All of the above

A key change in the 2023 report is that it now recommends long-acting muscarinic antagonist (LAMA)/long-acting beta-agonist (LABA) combination therapy for most patients (Groups B and E) as initial therapy, with bronchodilators recommended for patients in Group A. With this update, the combination of LABA and an inhaled corticosteroid (ICS) is only recommended to be considered in Group E it if blood eosinophils are ≥ 300 cells/μL.

The recommendation for group B patients is LABA/LAMA with the caveat that single inhaler therapy may be more convenient and effective than multiple inhalers. For group E patients with two or more moderate exacerbations or one or more leading to hospitalization, LABA/LAMA is recommended (with the same inhaler therapy caveat). With blood eosinophil levels at 300 cells/μL or higher, LABA/LAMA/ICS may be considered.

Source: Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2023 Report). © 2022, 2023 Global Initiative for Chronic Obstructive Lung Disease, Inc. Available at https://goldcopd.org/wp-content/uploads/2022/12/GOLD-2023-ver-1.1-2Dec2022_WMV.pdf Accessed January 2, 2023.

Pharmacological Therapy for Stable COPD

Pharmacological treatment for chronic obstructive pulmonary disease (COPD) **aims to alleviate symptoms and reduce the future risk of events such as exacerbations, disease progression and death**. The heterogeneity of COPD results in variable responses to pharmacological interventions. COPD treatment has evolved towards a precision medicine approach, integrating clinical and biomarker information in order to optimize treatment decisions for each individual.[41]

INITIAL PHARMACOLOGIC MANAGEMENT

The **GOLD 2023 Report** offers proposed clinical guidance, in the absence of high-quality clinical trial evidence, on initial pharmacologic management of **COPD**. The proposal is based on individual assessment of symptoms and exacerbation risk following the use of the ABE Assessment Tool, a revised version of the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) Assessment Tool that recognizes the clinical relevance of exacerbations independent of symptom level. The previous ABCD patient Assessment Tool for initial assessment and initiation of pharmacological management of COPD has been changed to the ABE Assessment Tool:[1]

- Groups A and B are unchanged, but groups C and D have been merged into a single group E to highlight the clinical relevance of exacerbations
- Patients categorized as group A have mMRC dyspnea scale scores of 0–1, a CAT score <10, and a history of zero or one moderate exacerbation not leading to hospitalization
- Patients in group B have mMRC scores ≥2, a CAT score ≥10, and a history of zero or one moderate exacerbation not leading to hospitalization
- Patients in group E have a history of ≥2 moderate exacerbations or ≥1 exacerbation leading to hospitalization, irrespective of their mMRC or CAT scores

The 2023 updates to initial pharmacological treatment and follow-up pharmacological treatment revise the positioning of LABA plus LAMA (long-acting muscarinic agonists) and LABA/ICS (inhaled corticosteroids). Among GOLD group A patients with 0 or 1 moderate exacerbations that do not lead to hospital admission, a bronchodilator is recommended.[1]

A **key change in the 2023** report is that it now recommends LAMA/LABA combination therapy for most patients (Groups B and E) as initial therapy, with bronchodilators recommended for patients in Group A. With this update, the combination of LABA and an inhaled corticosteroid (ICS) is only recommended to be considered in Group E it if blood eosinophils are ≥ 300 cells/μL.[1]

The **recommendation for group B patients is LABA/LAMA with the caveat that single inhaler therapy may be more convenient and effective than multiple inhalers**. For **group E patients with two or more moderate exacerbations or one or more leading to hospitalization, LABA/LAMA is recommended (with the same inhaler therapy caveat)**. With blood eosinophil levels at 300 cells/μL or higher, LABA/LAMA/ICS may be considered.[1]

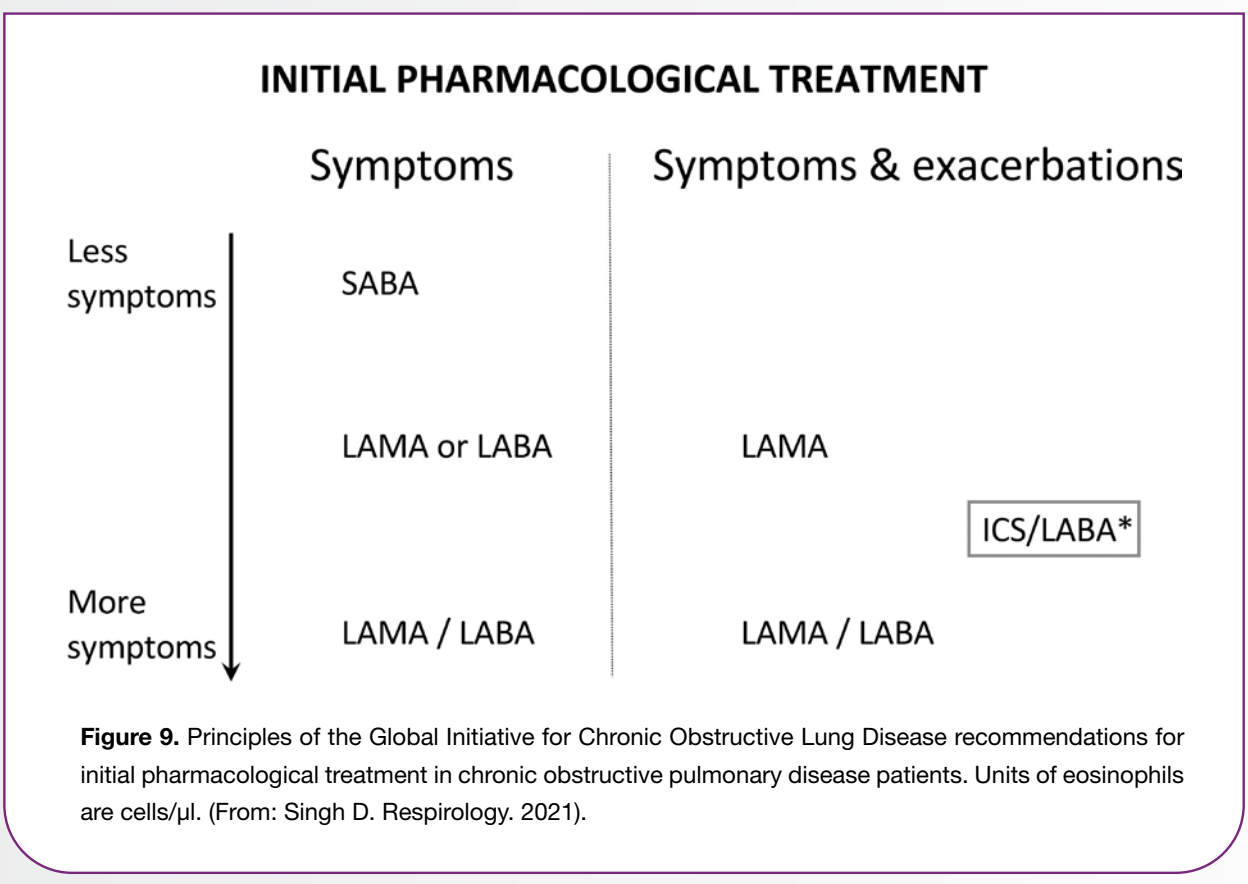


Figure 9. Principles of the Global Initiative for Chronic Obstructive Lung Disease recommendations for initial pharmacological treatment in chronic obstructive pulmonary disease patients. Units of eosinophils are cells/μl. (From: Singh D. Respirology. 2021).

FOLLOW-UP PHARMACOLOGIC MANAGEMENT

Recommendations are also made for follow-up therapy:[1]

- If the patient still has symptoms of shortness of breath while on only a single bronchodilator, then treatment should be increased to dual-bronchodilator therapy.
- If the patient has exacerbations on single bronchodilator therapy, with an eosinophil count < 300 cells/μL, treatment should be increased to dual-bronchodilator therapy
- If the eosinophil count is > 300 cells/μL, or if the patient is already on dual therapy and the eosinophil count is > 100 cells/μL, treatment should be escalated to triple therapy with a LABA/LAMA/ICS inhaler
- Roflumilast and azithromycin are mentioned as treatments for those with severe COPD and eosinophil counts < 100 cells/μL who are on dual therapy, or for select patients on triple therapy who are still having exacerbations

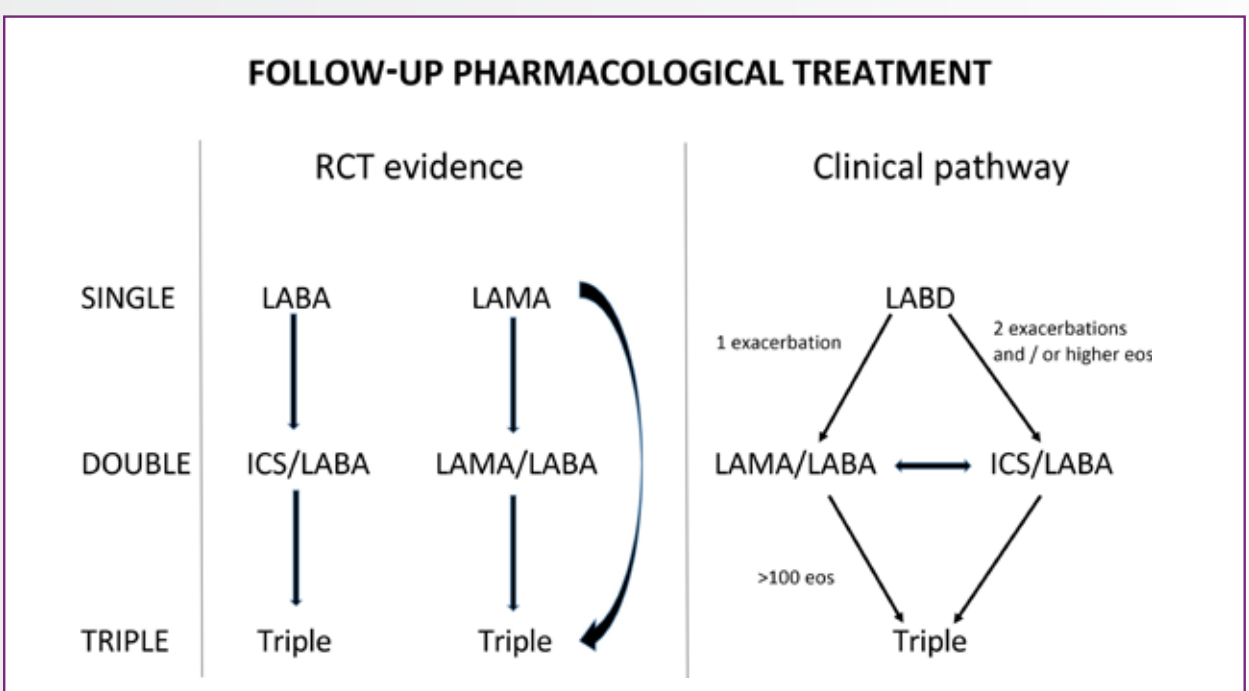


Figure 9. Follow-up pharmacological treatment (inhaled) for the management of chronic obstructive pulmonary disease patients with persistent exacerbations. Randomized controlled trial (RCT) evidence pathway shows treatment escalation steps supported by the results of RCTs (without subgroup eosinophil [eos] analysis). Clinical pathway represents the Global Initiative for Chronic Obstructive Lung Disease recommendations which incorporate levels of exacerbation risk and blood eos counts. Long-acting bronchodilator (LABD) monotherapy; inhaled corticosteroid (ICS) + long-acting beta-agonist (LABA) combination or dual LABD combination; triple, ICS + LABA + long-acting muscarinic antagonist. (From: Singh D. Respirology. 2021).

For further study, please visit https://onlinelibrary.wiley.com/doi/10.1111/resp.14046

Which of the below is correct?

a. Methylxanthiness block the bronchoconstrictor effects of acetylcholine

b. Beta $(\beta)_2$-adrenergic agonists mimic the functions of epinephrine

c. Antimuscarinic drugs act by inhibiting the recruitment and activation of cellular components of inflammation

d. PDE4 inhibitors inhibit phosphodiesterase

Correct Answer:

b. Beta $(\beta)_2$-adrenergic agonists mimic the functions of epinephrine

Beta $(\beta)_2$-adrenergic agonists are the frontline treatment for asthma and COPD diseases. They exert their pharmacologic effects via β_2-adrenoceptors that are predominantly present on airway smooth muscles but also exist on cardiac muscles, vascular endothelium, eosinophils, and lymphocytes. β_2-adrenoceptors agonists, including long-acting and short-acting β_2-agonists (LABA and SABA), are typically designed to mimic the functions of epinephrine by producing autonomic responses within the airway smooth muscle and to limit the stimulation to β_2-adrenoceptors outside the airway smooth muscles as much as possible to reduce adverse effects.

Antimuscarinic drugs block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle.

Methylxanthines, which include aminophylline and theophylline, act by inhibiting phosphodiesterase. They can be considered as an alternative therapy in patients with COPD who do not respond to traditional treatments. There is limited evidence supporting their use, and numerous studies found conflicting results in terms of their efficacy and safety.

Among drugs that inhibit the recruitment and activation of cellular components of inflammation, PDE4 inhibitors are certainly the most widely studied. At present, only roflumilast has been approved for clinical use and, in any case, it is burdened by side effects that considerably reduce patient compliance.

Sources: 1. Amegadzie JE, Gamble JM, Farrell J, Gao Z. Association between Inhaled β_2-agonists Initiation and Risk of Major Adverse Cardiovascular Events: A Population-based Nested Case-Control Study. Int J Chron Obstruct Pulmon Dis. 2022 May 20;17:1205-1217. **2.** Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2023 Report). © 2022, 2023 Global Initiative for Chronic Obstructive Lung Disease, Inc. Available at https://goldcopd.org/wp-content/uploads/2022/12/GOLD-2023-ver-1.1-2Dec2022_WMV.pdf Accessed January 2, 2023. **3.** Rosenwasser Y, Berger I, Loewy ZG. Therapeutic Approaches for Chronic Obstructive Pulmonary Disease (COPD) Exacerbations. Pathogens. 2022 Dec 10;11(12):1513. **4.** Cazzola M, Ora J, Calzetta L, Rogliani P, Matera MG. The future of inhalation therapy in chronic obstructive pulmonary disease. Curr Res Pharmacol Drug Discov. 2022 Feb 17;3:100092

Medications Used in COPD Treatment

In recent years, significant progress has been made in the development of new pharmacological and surgical tools to treat COPD, while the rates of prevalence and mortality owing to COPD are still noticeable.[39]

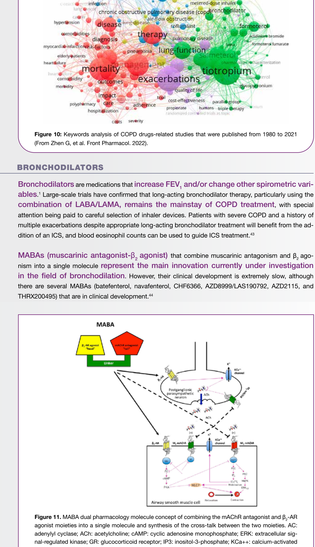


Figure 10: Keywords analysis of COPD drugs-related studies that were published from 1980 to 2021 (From Zhen G, et al. Front Pharmacol. 2022).

BRONCHODILATORS

Bronchodilators are medications that increase FEV, and/or change other spirometric variables.[1] Large-scale trials have confirmed that long-acting bronchodilator therapy, particularly using the combination of LABA/LAMA, remains the mainstay of COPD treatment, with special attention being paid to careful selection of inhaler devices. Patients with severe COPD and a history of multiple exacerbations despite appropriate long-acting bronchodilator treatment will benefit from the addition of an ICS, and blood eosinophil counts can be used to guide ICS treatment.[43]

MABAs (muscarinic antagonist-β_2 agonist) that combine muscarinic antagonism and β_2 agonism into a single molecule represent the main innovation currently under investigation in the field of bronchodilation. However, their clinical development is extremely slow, although there are several MABAs (batefenterol, navafenterol, CHF6366, AZD8999/LAS190792, AZD2115, and THR0200495) that are in clinical development.[44]

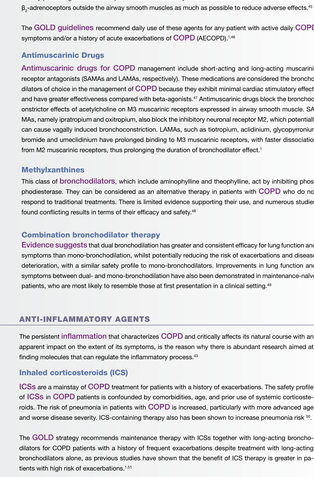


Figure 11. MABA dual pharmacology molecule concept of combining the mAChR antagonist and β_2-AR agonist moieties into a single molecule and synthesis of the cross-talk between the two moieties. AC: adenylyl cyclase; ACh: acetylcholine; cAMP: cyclic adenosine monophosphate; ERK: extracellular signal-regulated kinase; GR: glucocorticoid receptor; IP3: inositol-3-phosphate; KCa++: calcium-activated potassium channel; mAChR: muscarinic ACh receptor; MAPK: p38 mitogen-activated protein kinase; MLCP: myosin light chain phosphatase; PKA: protein kinase A; PKC, protein kinase C; PLC: phospholipase C; β2-AR: β2-adrenoceptor. Solid line, activation; dotted line, inhibition. (From: Cazzola M, et al. Curr Res Pharmacol Drug Discov. 2022).

Beta2-agonists

Beta (β_2)-adrenergic agonists are the frontline treatment for asthma and COPD diseases. They exert their pharmacologic effects via β_2-adrenoceptors that are predominantly present on airway smooth muscles but also exist on cardiac muscles, vascular endothelium, eosinophils, and lymphocytes. β_2-adrenoceptors agonists, including LABA and SABA, are typically designed to mimic the functions of epinephrine by producing autonomic responses within the airway smooth muscle and to limit the stimulation to β_2-adrenoceptors outside the airway smooth muscles as much as possible to reduce adverse effects.[45]

The GOLD guidelines recommend daily use of these agents for any patient with active daily COPD symptoms and/or a history of acute exacerbations of COPD (AECOPD).[1,46]

Antimuscarinic Drugs

Antimuscarinic drugs for COPD management include short-acting and long-acting muscarinic receptor antagonists (SAMAs and LAMAs, respectively). These medications are considered the bronchodilators of choice in the management of COPD as they exhibit minimal cardiac stimulatory effects and have greater effectiveness compared with beta-agonists.[47] Antimuscarinic drugs block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle. SAMAs, namely ipratropium and oxitropium, also block the inhibitory neuronal receptor M2, which potentially can cause vagally induced bronchoconstriction. LAMAs, such as tiotropium, aclidinium, glycopyrronium bromide and umeclidinium have prolonged binding to M3 muscarinic receptors, with faster dissociation from M2 muscarinic receptors, thus prolonging the duration of bronchodilator effect.[1]

Methylxanthines

This class of bronchodilators, which include aminophylline and theophylline, act by inhibiting phosphodiesterase. They can be considered as an alternative therapy in patients with COPD who do not respond to traditional treatments. There is limited evidence supporting their use, and numerous studies found conflicting results in terms of their efficacy and safety.[48]

Combination bronchodilator therapy

Evidence suggests that dual bronchodilation has greater and consistent efficacy for lung function and symptoms than mono-bronchodilation, whilst potentially reducing the risk of exacerbations and disease deterioration, with a similar safety profile to mono-bronchodilators. Improvements in lung function and symptoms between dual- and mono-bronchodilation have also been demonstrated in maintenance-naïve patients, who are most likely to resemble those at first presentation in a clinical setting.[49]

ANTI-INFLAMMATORY AGENTS

The persistent inflammation that characterizes COPD and critically affects its natural course with an apparent impact on the extent of its symptoms, is the reason why there is abundant research aimed at finding molecules that can regulate the inflammatory process.[43]

Inhaled corticosteroids (ICS)

ICSs are a mainstay of COPD treatment for patients with a history of exacerbations. The safety profile of ICSs in COPD patients is confounded by comorbidities, age, and prior use of systemic corticosteroids. The risk of pneumonia in patients with COPD is increased, particularly with more advanced age and worse disease severity. ICS-containing therapy also has been shown to increase pneumonia risk [50].

The GOLD strategy recommends maintenance therapy with ICSs together with long-acting bronchodilators for COPD patients with a history of frequent exacerbations despite treatment with long-acting bronchodilators alone, as previous studies have shown that the benefit of ICS therapy is greater in patients with high risk of exacerbations.[1,51]

Oral glucocorticoids

Oral glucocorticosteroids (OCS) are recommended to patients with COPD during acute exacerbations, and most COPD exacerbations can safely be managed in the outpatient setting. OCS have been found to shorten the length of hospital stays, improve lung function, and reduce the risk of early relapse and treatment failure in patients with non-pneumonia exacerbation. However, OCS use is associated with a number of adverse effects including hyperglycemia, fluid retention, weight gain, hypertension, diabetes mellitus, adrenal suppression, deep vein thrombosis, osteoporosis and increased fracture risk.[52]

Phosphodiesterase-4 (PDE4) inhibitors

Among drugs that inhibit the recruitment and activation of cellular components of inflammation, PDE4 inhibitors are certainly the most widely studied. At present, only roflumilast has been approved for clinical use and, in any case, it is burdened by side effects that considerably reduce patient compliance.[43]

TRIPLE INHALED THERAPY

During the past two decades, ICS/LABA combinations were broadly used for the treatment of COPD. Their use was based on large studies showing that this therapeutic scheme was more effective compared to placebo and to LABA monotherapy on the reduction of COPD exacerbations and on the improvement of lung function and health-related quality of life. However, ICS/LABA combinations have been shown to be inferior compared to the combination of two bronchodilators (LABA/LAMA) regarding lung function and health status improvements and exacerbation reduction.[53]

Although the use of LABA/LAMA/ICS with different inhalation devices, mostly as LABA/ICS plus LAMA and infrequently as LABA/LAMA plus ICS, was an option, nowadays the so-called triple therapy represents the combination of a LABA, a LAMA and an ICS in a single inhalation device. The different clinical trials available for three fixed combinations showed both better efficacy and safety compared to mono-components and dual combinations. Interestingly, the implementation of this new treatment strategy remains a real challenge for the physician since it is often difficult to clarify the population who really needs to be treated with triple therapy and to avoid overtreatment.[52]

Currently, three different triple combinations are been studied for the treatment of stable COPD: Glycopyrronium/Formoterol fumarate/Beclomethasone dipropionate (GFB), Fluticasone furoate/Vilanterol/Umeclidinium (FVU) and Budesonide/Glycopyrrolate/Formoterol fumarate (BGF).[52]

ANTIBIOTICS

Antibiotics are frequently prescribed for acute exacerbations of COPD (AECOPD) even though most do not have a bacterial aetiology.[54]

- The 2022 GOLD international guideline recommends use of antibiotics for acute exacerbations of COPD (AECOPD) in patients with increased sputum purulence who have one or both of increased dyspnoea and increased sputum volume, as well as patients that require mechanical ventilation.[1,2]
- The U.K. NICE guidance advises prescribers to consider the severity of symptoms, particularly sputum colour changes and increases in volume or thickness, whether they may need to go to hospital, previous exacerbation and hospitalization history, and the risk of developing complications, previous sputum culture results, and the risk of antimicrobial resistance when considering whether or not to prescribe antibiotics for patients with AECOPD.[3,4]

Regular use of some antibiotics may reduce exacerbation rate. A Cochrane analysis concluded that use of prophylactic macrolide antibiotics for a period of up to 12 months is likely to reduce the number of patients with one or more exacerbations, exacerbation frequency, increase the median time to first exacerbation and improve health-related quality of life. Benefits appear to be driven by continuous and intermittent macrolide regimens, with pulsed regimens being less effective. However, the benefits need to be balanced against the risk of harm, notably antibiotic resistance, and the cost and adherence implications for the patient and the health care system, as well as potential costs of monitoring for adverse effects.[55]

MUCOLYTIC (MUCOKINETICS, MUCOREGULATORS) AND ANTIOXIDANT AGENTS (NAC, CARBOCYSTEINE)

Long-term mucoactive/antioxidant therapy for chronic bronchitis or COPD patients should be initiated as long as patients complain of cough with sputum or dyspnea. If the patient with the evidence of COPD lung function complains of cough with sputum since childhood and if computed tomography (CT) scan shows evidence of bronchiectasis, patients do need mucoactive/antioxidant therapy. COPD patients whose FEV,% is more than 50% but who complain of cough with sputum, patients who have a problem sleeping due to expectoration symptom and asthma or allergy could be excluded. COPD patients with lung function classes 3 and 4, more than 2 clinical visits, and GOLD C or D group patients who do not have ICS inhalation or who show a combination with bronchiectasis need treatment.[56]

An analysis of 72 articles, published in peer-reviewed journals with high impact factor provided significant insight and increase the knowledge about COPD considering the important contribution of carbocysteine in reducing exacerbations via multiple mechanisms. Carbocysteine is in fact able to modulate mucins and ciliary functions, and to counteract viral and bacterial infections as well as oxidative stress, offering cytoprotective effects. Furthermore, carbocysteine improves steroid responsiveness and exerts anti-inflammatory activity. This analysis demonstrated that the use of carbocysteine in COPD patients represents a well-tolerated treatment with a favorable safety profile, and might contribute to a better quality of life for patients suffering from this serious illness.[57]

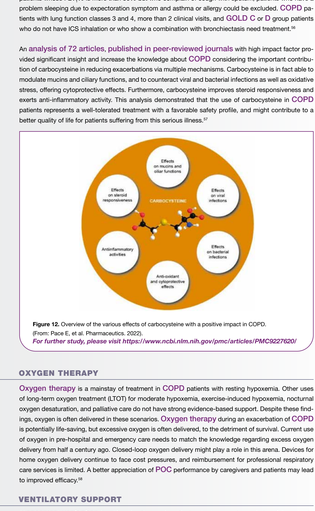


Figure 12. Overview of the various effects of carbocysteine with a positive impact in COPD. (From: Pace E, et al. Pharmaceutics. 2022).
For further study, please visit https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9227620/

OXYGEN THERAPY

Oxygen therapy is a mainstay of treatment in COPD patients with resting hypoxemia. Other uses of long-term oxygen treatment (LTOT) for moderate hypoxemia, exercise-induced hypoxemia, nocturnal oxygen desaturation, and palliative care do not have strong evidence-based support. Despite these findings, oxygen is often delivered in these scenarios. Oxygen therapy during an exacerbation of COPD is potentially life-saving, but excessive oxygen is often delivered, to the detriment of survival. Current use of oxygen in pre-hospital and emergency care needs to match the knowledge regarding excess oxygen delivery from half a century ago. Closed-loop oxygen delivery might play a role in this arena. Devices for home oxygen delivery continue to face cost pressures, and reimbursement for professional respiratory care services is limited. A better appreciation of POC performance by caregivers and patients may lead to improved efficacy.[58]

VENTILATORY SUPPORT

Mechanical ventilation is a lifesaving therapy in patients who have acute respiratory failure due to COPD. Mechanical ventilation either invasive or non-invasive has an important role in the management of AECOPD. AECOPD required hospitalization had increased mortality and poor prognosis. Ventilatory management success related to understanding physiopathology of the disease. Clinicians must be aware of deterioration of clinical signs of COPD patients. The most appropriate treatment should be performed at optimal time. Some COPD patients are at high risk for prolonged mechanical ventilation due to COPD being a progressive disease.[59]

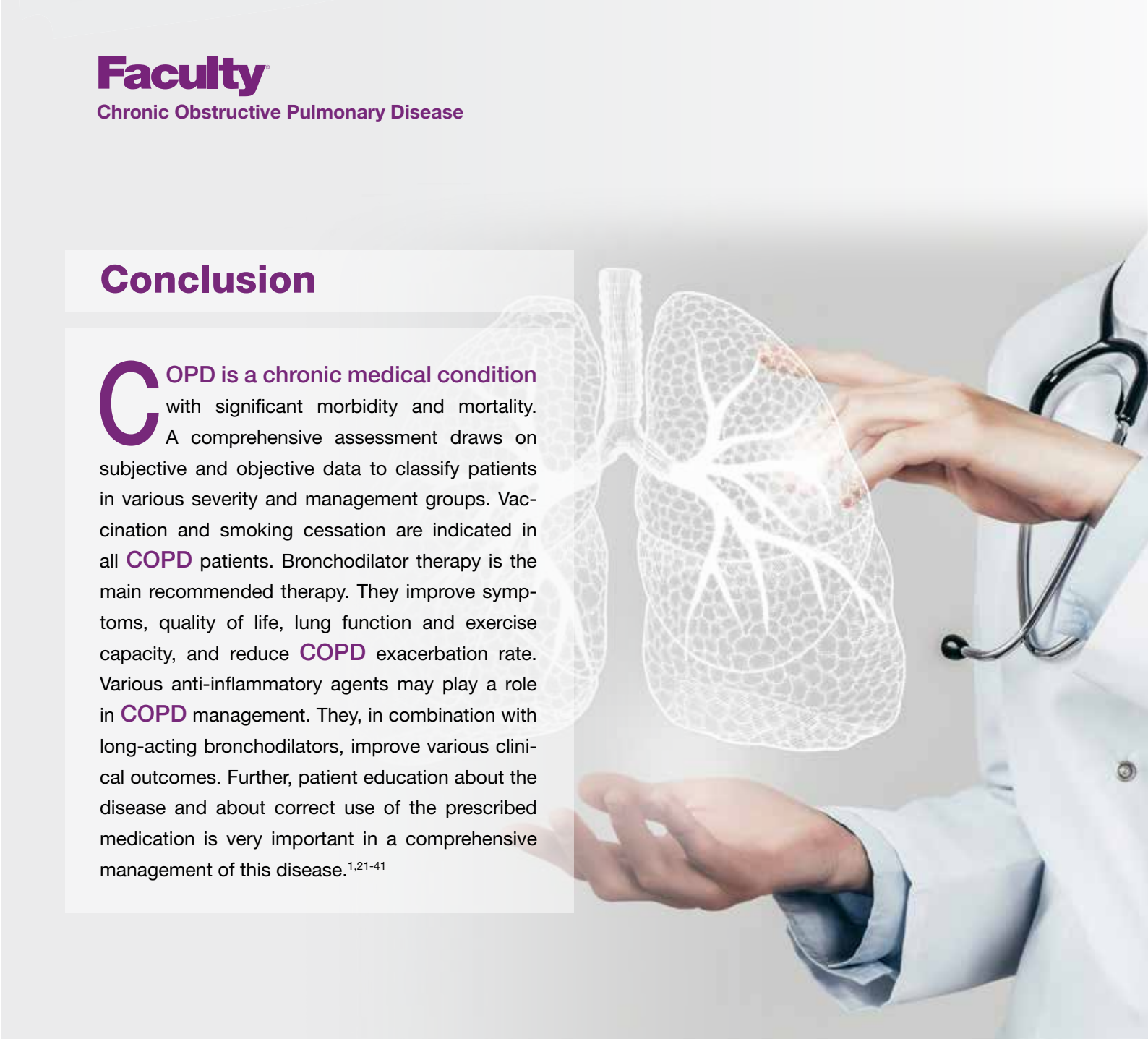
Pulmonary Rehabilitation

Pulmonary rehabilitation (PR) improves exercise capacity, health-related quality of life (HRQoL) and dyspnea in **COPD patients**. Maintenance programs can sustain the benefits for 12 to 24 months.[60]

Clinical guidelines for the management of people with **COPD** recommend that PR should be provided to people with stable **COPD** who experience symptoms during daily life, as well as during or soon after an exacerbation of the disease. Despite guideline recommendations and robust evidence to support its effectiveness, PR is underused. Healthcare professionals (e.g. Physicians, General Practitioner's, Physiotherapists) report barriers to PR referral such as limited knowledge of its benefits, uncertainty around program details (i.e. referral processes, location, content and duration of the program), and limited time to discuss and refer to PR. The failure to discuss and advocate for PR in the in-patient and out-patient setting leaves people with COPD largely unaware of both the existence of PR programs and its health benefits.[61]

Conclusion

COPD is a chronic medical condition with significant morbidity and mortality. A comprehensive assessment draws on subjective and objective data to classify patients in various severity and management groups. Vaccination and smoking cessation are indicated in all COPD patients. Bronchodilator therapy is the main recommended therapy. They improve symptoms, quality of life, lung function and exercise capacity, and reduce COPD exacerbation rate. Various anti-inflammatory agents may play a role in COPD management. They, in combination with long-acting bronchodilators, improve various clinical outcomes. Further, patient education about the disease and about correct use of the prescribed medication is very important in a comprehensive management of this disease.[1,21-41]



References

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2023 Report). © 2022, 2023 Global Initiative for Chronic Obstructive Lung Disease, Inc. Available at https://goldcopd.org/wp-content/uploads/2022/12/GOLD-2023-ver-1.1-2Dec2022_WMV.pdf Accessed January 2, 2023.
2. European Lung White Book. Chronic Obstructive Lung Disease. Available at https://www.erswhitebook.org/chapters/chronic-obstructive-pulmonary-disease/
3. Yousuf A, McAuley H, Elneima O, Brightling CE. The different phenotypes of COPD. Br Med Bull. 2021 Mar 25;137(1):82-97.
4. Curtis JL, Cho MH, Hansel NN. COPD : Pathogenesis and Natural History. In: Murray & Nadel's Textbook of Respiratory Medicine, 63, 850-869.e12. Seventh Edition. Copyright © 2022 by Elsevier, Inc
5. Terence Ho, Ruth P. Cusack, Nagendra Chaudhary, Imran Satia, Om P. Kurmi. Under- and over-diagnosis of COPD: a global perspective. Breathe 2019 15: 24-35.
6. Safiri S, Carson-Chahhoud K, Noori M, Nejadghaderi SA, Sullman MJM, Ahmadian Heris J, Ansarin K, Mansournia MA, Collins GS, Kolahi AA, Kaufman JS. Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019. BMJ. 2022 Jul 27;378:e069679.
7. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020 Oct 17;396(10258):1204-1222.
8. Halpin DMG, Vogelmeier CF, Agusti A. Lung Health for All: Chronic Obstructive Lung Disease and World Lung Day 2022. Am J Respir Crit Care Med. 2022 Sep 15;206(6):669-671.
9. Antuni JD, Barnes PJ. Evaluation of individuals at risk for COPD: Beyond the scope of the Global initiative for chronic Obstructive Lung Disease. Chronic Obstr Pulm Dis. 2016; 3(3): 653-667.
10. Blanc PD, Annesi-Maesano I, Balmes JR, Cummings KJ, Fishwick D, Miedinger D, Murgia N, Naidoo RN, Reynolds CJ, Sigsgaard T, Torén K, Vinnikov D, Redlich CA. The Occupational Burden of Nonmalignant Respiratory Diseases. An Official American Thoracic Society and European Respiratory Society Statement. Am J Respir Crit Care Med. 2019 Jun 1;199(11):1312-1334.
11. De Matteis S, Jarvis D, Darnton A, Hutchings S, Sadhra S, Fishwick D, Rushton L, Cullinan P. The occupations at increased risk of COPD: analysis of lifetime job-histories in the population-based UK Biobank Cohort. Eur Respir J. 2019 Jul 18;54(1):1900186.
12. Office for National Statistics. Standard Occupational Classification 2000. Available at: https://www.ons.gov.uk/methodology/classificationsandstandards/standardoccupationalclassificationsoc/socarchive. Accessed: January 2, 2023.
13. Getahun, Biruk, Bekel, Abebe. "Work - Related Chronic Obstructive Pulmonary Disease" In Chronic Obstructive Pulmonary Disease: A Current Conspectus, edited by Kian Ong. London: IntechOpen, 2021. 10.5772/intechopen.96131
14. Capistrano SJ, van Reyk D, Chen H, Oliver BG. Evidence of Biomass Smoke Exposure as a Causative Factor for the Development of COPD. Toxics. 2017 Dec 1;5(4):36.
15. Silverman EK. Genetics of COPD. Annu Rev Physiol. 2020 Feb 10;82:413-431.
16. Sahni S, Talwar A, Khanijo S, Talwar A. Socioeconomic status and its relationship to chronic respiratory disease. Adv Respir Med. 2017;85(2):97-108.
17. Borné Y, Ashraf W, Zaigham S, Frantz S. Socioeconomic circumstances and incidence of chronic obstructive pulmonary disease (COPD) in an urban population in Sweden. COPD. 2019 Feb;16(1):51-57.
18. Bui DS, Lodge CJ, Burgess JA, Lowe AJ, Perret J, Bui MQ, Bowatte G, Gurrin L, Johns DP, Thompson BR, Hamilton GS, Frith PA, James AL, Thomas PS, Jarvis D, Svanes C, Russell M, Morrison SC, Feather I, Allen KJ, Wood-Baker R, Hopper J, Giles GG, Abramson MJ, Walters EH, Matheson MC, Dharmage SC. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. Lancet Respir Med. 2018 Jul;6(7):535-544.
19. Belgrave DCM, Granell R, Turner SW, Curtin JA, Buchan IE, Le Souëf PN, Simpson A, Henderson AJ, Custovic A. Lung function trajectories from pre-school age to adulthood and their associations with early life factors: a retrospective analysis of three population-based birth cohort studies. Lancet Respir Med. 2018 Jul;6(7):526-534.
20. Choi JY, Rhee CK. Diagnosis and Treatment of Early Chronic Obstructive Lung Disease (COPD). J Clin Med. 2020 Oct 26;9(11):3426. doi: 10.3390/jcm9113426.
21. Hayden LP, Cho MH, Raby BA, Beaty TH, Silverman EK, Hersh CP; COPDGene Investigators. Childhood asthma is associated with COPD and known asthma variants in COPDGene: a genome-wide association study. Respir Res. 2018 Oct 29;19(1):209.
22. Marcon A, Locatelli F, Dharmage SC, Svanes C, Heinrich J, Leynaert B, Burney P, Corsico A, Caliskan G, Calciano L, Gislason T, Janson C, Jarvis D, Jõgi R, Lytras T, Malinovschi A, Probst-Hensch N, Toren K, Casas L, Verlato G, Garcia-Aymerich J, Accordini S; Ageing Lungs in European Cohorts (ALEC) study. The coexistence of asthma and COPD: risk factors, clinical history and lung function trajectories. Eur Respir J. 2021 Nov 25;58(5):2004656.
23. Tian PW, Wen FQ. Clinical significance of airway mucus hypersecretion in chronic obstructive pulmonary disease. J Transl Int Med. 2015 Jun-Sep;3(3):89-92.
24. Whittaker H, Nordon C, Rubino A, Morris T, Xu Y, De Nigris E, Müllerová H, Quint JK. Frequency and severity of respiratory infections prior to COPD diagnosis and risk of subsequent postdiagnosis COPD exacerbations and mortality: EXACOS-UK health care data study. Thorax. 2022 Oct 31:thoraxjnl-2022-219039.
25. Buendia-Roldan I, Palma-Lopez A, Chan-Padilla D, Herrera I, Maldonado M, Fernández R, Martínez-Briseño D, Mejia M, Selman M. Risk factors associated with the detection of pulmonary emphysema in older asymptomatic respiratory subjects. BMC Pulm Med. 2020 Jun 9;20(1):164.
26. Timbadia PJ, Fagan JB. Chronic Obstructive Pulmonary Disease. In: Kellerman RD and Rakel DP (Eds) Conn's Current Therapy 2023, 897-902 Copyright © 2023 by Elsevier, Inc. All rights reserved.
27. Agarwal AK, Raja A, Brown BD. Chronic Obstructive Pulmonary Disease. [Updated 2022 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559281/
28. Munari AB, Gulart AA, Dos Santos K, Venâncio RS, Karloh M, Mayer AF. Modified Medical Research Council Dyspnea Scale in GOLD Classification Better Reflects Physical Activities of Daily Living. Respir Care. 2018 Jan;63(1):77-85.
29. Thomashow B, Stiegler M, Criner GJ, Dransfield MT, Halpin DMG, Han MK, Lange P, Martinez FJ, Midwinter D, Singh D, Tabberer M, Wise RA, Lipson DA, Jones P. Higher COPD Assessment Test Score Associated With Greater Exacerbations Risk: A Post Hoc Analysis of the IMPACT Trial. Chronic Obstr Pulm Dis. 2022 Jan 27;9(1):68-79.
30. Bouwens JDM, Bischoff EWMA, In 't Veen JCCM, Schermer TR. Diagnostic differentiation between asthma and COPD in primary care using lung function testing. NPJ Prim Care Respir Med. 2022 Sep 5;32(1):32.
31. Mekov E, Nuñez A, Sin DD, Ichinose M, Rhee CK, Maselli DJ, Coté A, Suppli Ulrik C, Maltais F, Anzueto A, Miravitlles M. Update on Asthma-COPD Overlap (ACO): A Narrative Review. Int J Chron Obstruct Pulmon Dis. 2021 Jun 17;16:1783-1799.
32. Andelius DK, Hilberg O, Ibsen R, Løkke A. Pharmacological smoking cessation of adults aged 30-50 years with COPD. NPJ Prim Care Respir Med. 2022 Oct 8;32(1):39.
33. Agrawal, R., Moghtader, S., Ayyala, U., Bandi, V., Sharafkhaneh, A. Update on management of stable chronic obstructive pulmonary disease. J Thorac Dis 2019;11(Suppl 14):S1800-S1809
34. Lee PN, Fariss MW. A systematic review of possible serious adverse health effects of nicotine replacement therapy. Arch Toxicol 2017;91:1565-94.
35. Worku D, Worku E. A narrative review evaluating the safety and efficacy of e-cigarettes as a newly marketed smoking cessation tool. SAGE Open Med. 2019 Aug 18;7:2050312119871405.
36. Quigley JM, Walsh C, Lee C, Long J, Kennelly H, McCarthy A, Kavanagh P. Efficacy and safety of electronic cigarettes as a smoking cessation intervention: A systematic review and network meta-analysis. Tob Prev Cessat. 2021 Nov 22;7:69.
37. Shang X, Guo K, E F, Deng X, Wang Y, Wang Z, Wu Y, Xu M, Yang C, Li X, Yang K. Pharmacological interventions on smoking cessation: A systematic review and network meta-analysis. Front Pharmacol. 2022 Oct 24;13:1012433.
38. Ignatova GL, Avdeev SN, Antonov VN. Comparative effectiveness of pneumococcal vaccination with PPV23 and PCV13 in COPD patients over a 5-year follow-up cohort study. Sci Rep. 2021 Aug 5;11(1):15948.
39. Southworth T, Jackson N, Singh D. Airway immune responses to COVID-19 vaccination in COPD patients and healthy subjects. Eur Respir J. 2022 Aug 25;60(2):2200497.
40. Xiang X, Huang L, Fang Y, Cai S, Zhang M. Physical activity and chronic obstructive pulmonary disease: a scoping review. BMC Pulm Med. 2022 Aug 5;22(1):301.
41. Singh D. Pharmacological treatment of stable chronic obstructive pulmonary disease. Respirology. 2021 Jul;26(7):643-651.
42. Zhen G, Yingying L, Jingcheng D. Drug Therapies for COPD: A Bibliometric Review From 1980 to 2021. Front Pharmacol. 2022 Apr 20;13:820086.
43. Yamada H, Matsumoto I, Makita N, Arita Y, Hayashi N, Mitsuoka K, Tashiro N, Hizawa N. Effect of timing of bronchodilator therapy initiation on exacerbations in patients with chronic obstructive pulmonary disease: a retrospective cohort study. Respir Res. 2022 Sep 19;23(1):255.
44. Cazzola M, Ora J, Calzetta L, Rogliani P, Matera MG. The future of inhalation therapy in chronic obstructive pulmonary disease. Curr Res Pharmacol Drug Discov. 2022 Feb 17;3:100092
45. Amegadzie JE, Gamble JM, Farrell J, Gao Z. Association between Inhaled β2-agonists Initiation and Risk of Major Adverse Cardiovascular Events: A Population-based Nested Case-Control Study. Int J Chron Obstruct Pulmon Dis. 2022 May 20;17:1205-1217.
46. Burkes RM, Panos RJ. Ultra Long-Acting β-Agonists in Chronic Obstructive Pulmonary Disease. J Exp Pharmacol. 2020 Dec 14;12:589-602.
47. Nguyen T, George M. Antimuscarinic Medications for Chronic Obstructive Pulmonary Disease. Prescription Pad. 2021;17(7):894-895.
48. Rosenwasser Y, Berger I, Loewy ZG. Therapeutic Approaches for Chronic Obstructive Pulmonary Disease (COPD) Exacerbations. Pathogens. 2022 Dec 10;11(12):1513.
49. Singh D, Donohue JF, Boucot IH, Barnes NC, Compton C, Martinez FJ. Future concepts in bronchodilation for COPD: dual- versus monotherapy. Eur Respir Rev. 2021 Jun 1;30(160):210023doi: 10.1183/16000617.0023-2021. PMID: 34415847; PMCID: PMC9489138.
50. Tashkin DP, Strange C. Inhaled corticosteroids for chronic obstructive pulmonary disease: what is their role in therapy? Int J Chron Obstruct Pulmon Dis. 2018 Aug 27;13:2587-2601.
51. Savran O, Godtfredsen N, Sørensen T, Jensen C, Ulrik CS. COPD patients prescribed inhaled corticosteroid in primary care: time for re-assessment based on exacerbation rate and blood eosinophils? Respir Res. 2021 Feb 12;22(1):54.
52. Sivapalan P, Ingebrigtsen TS, Rasmussen DB, Sørensen R, Rasmussen CM, Jensen CB, Allin KH, Eklöf J, Seersholm N, Vestbo J, Jensen JS. COPD exacerbations: the impact of long versus short courses of oral corticosteroids on mortality and pneumonia: nationwide data on 67 000 patients with COPD followed for 12 months. BMJ Open Respir Res. 2019 Mar 30;6(1):e000407.
53. Papaioannou AI, Loukides S, Bakakos P, Kosmas EN, Rovina N, Steiropoulos P, Fouka E, Hillas G, Patentalakis G, Kouvela M, Tzanakis N. Dual Bronchodilator in the Era of Triple Therapy. Int J Chron Obstruct Pulmon Dis. 2020 Oct 28;15:2695-2705.
54. Hoult G, Gillespie D, Wilkinson TMA, Thomas M, Francis NA. Biomarkers to guide the use of antibiotics for acute exacerbations of COPD (AECOPD): a systematic review and meta-analysis. BMC Pulm Med. 2022 May 13;22(1):194.
55. Herath SC, Normansell R, Maisey S, Poole P. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2018 Oct 30;10(10):CD009764.
56. Yan X, Song Y, Shen C, Xu W, Chen L, Zhang J, Liu H, Huang M, Lai G, Qian G, Wang J, Ye X, Zheng J, Bai C. Mucoactive and antioxidant medicines for COPD: consensus of a group of Chinese pulmonary physicians. Int J Chron Obstruct Pulmon Dis. 2017 Mar 22;12:803-812.
57. Pace E, Cerveri I, Lacedonia D, Paone G, Sanduzzi Zamparelli A, Sorbo R, Allegretti M, Lanata L, Scaglione F. Clinical Efficacy of Carbocysteine in COPD: Beyond the Mucolytic Action. Pharmaceutics. 2022 Jun 14;14(6):1261.
58. Branson RD. Oxygen Therapy in COPD. Respiratory Care June 2018, 63 (6) 734-748
59. Ediboglu O. Mechanical Ventilation for Patients with COPD. In Chronic Obstructive Pulmonary Disease: A Current Conspectus, edited by Kian Ong. London: IntechOpen, 2021. 10.5772/intechopen.96633. Available at https://www.intechopen.com/chapters/75664 Accessed January 11, 2023.
60. Blervaque L, Préfaut C, Forthin H, Maffre F, Bourrelier M, Héraud N, Catteau M, Pomiès P, Jaffuel D, Molinari N, Hayot M, Gouzi F. Efficacy of a long-term pulmonary rehabilitation maintenance program for COPD patients in a real-life setting: a 5-year cohort study. Respir Res. 2021 Mar 10;22(1):79.
61. Hug S, Cavalheri V, Gucciardi DF, Norman R, Hill K. OPTImising the implementation of pulMonary rehAbiLitation in people with chronic obstructive pulmonary disease (the OPTIMAL study): mixed methods study protocol. BMC Pulm Med. 2020 Nov 2;20(1):286.