South African Family Practice 2016; 58(1):19-26

S Afr Fam Pract
ISSN 2078-6190 EISSN 2078-6204

REVIEW

"Alpha-1, are you in? (C)harlie (O)scar (P)appa (D)elta, over!"

GL Muntingh[1*]

[1]*Department of Pharmacology, Faculty of Health Sciences, School of Medicine, University of Pretoria*
[*]*Corresponding author, email: george.muntingh@up.ac.za*

Abstract

Chronic obstructive pulmonary disease (COPD) is characterised by chronically poor air flow. Typically, it worsens over time. The main symptoms include shortness of breath, coughing and sputum production. Most people with chronic bronchitis have COPD. Tobacco smoking is the most common cause of COPD. A number of other factors, such as air pollution and genetics, play a smaller role. One of the common sources of air pollution is poorly vented cooking and heating fires in the developing world. Long-term exposure to these irritants causes an inflammatory response in the lungs, resulting in narrowing of the small airways and breakdown of the lung tissue, leading to emphysema. Genetic involvement, i.e. alpha-1 antitrypsin deficiency, is now a recognised cause. The diagnosis is based on poor air flow, as measured by lung function tests. In contrast to asthma, the air flow reduction does not improve significantly with the administration of a bronchodilator. COPD can be prevented by reducing exposure to known environmental risk factors. This includes an effort to decrease the rate of smoking and to improve indoor and outdoor air quality. COPD treatment includes stopping smoking, vaccinations, rehabilitation, and often inhaled bronchodilators and steroids. Some people may benefit from long-term oxygen therapy or lung transplantation. Increased use of medication and hospitalisation may be needed in those who have periods of acute worsening. Worldwide, COPD effects 329 million people, or nearly 5% of the population. In 2013, it resulted in 2.9 million deaths, up from 2.4 million deaths in 1990. The number of deaths is projected to increase owing to higher smoking rates and an ageing population in many countries. New treatments are also emerging very slowly.

Keywords: AAT, apha-1 antitrypsin, COPD, emphysema, exacerbations, smoking

Introduction

"Cold morning today, doctor", a 60-year old patient manages to so say before sitting down with effort, clutching a crumbled packet of Lucky Strikes in his left hand, complaining that he's been coughing for nearly three months now, for two years, and that this "sputum never stops". He continues to mumble something to the effect that his breathing requires effort and that he feels out of breath and can't "get enough air in". The patient has a pink complexion, his respiratory rate is a little high and he has pursed lips. Perhaps the diagnosis is smoker's lung or "pink puffer". However, he then explains that sometimes his lips are blue and that his ankles swell a bit. Could the diagnosis be "blue bloater"? However, this terminology is no longer accepted as useful as most patients with chronic obstructive pulmonary disease (COPD) have a combination of both emphysema and chronic bronchitis.[1,2]

History of emphysema

The word "emphysema" is derived from the Greek word, *emphusan,* and means "puff up" or to "inflate".[3]

Figure 1: Giovanni Battista Morgagni, who provided one of the earliest recorded descriptions of emphysema in 1769

One of the earliest descriptions of probable emphysema was made in 1679 by Bonet of a condition of "voluminous lungs". In 1769, Morgagni (Figure 1) described lungs which were"turgid, particularly from air".[4,5]

In 1721, the first drawings of this condition were made by Ruysh.[5] These were followed with pictures by Baillie in 1789, and descriptions of the destructive nature of the condition. In 1814, Badham used "catarrh" to describe the coughing and excess mucus in chronic bronchitis. Laënnec, the physician who invented the stethoscope, used the term "emphysema" in his book, *A treatise on the diseases of the chest and of mediate auscultation*, (1837) to describe lungs which did not collapse when he opened the chest during an autopsy.

Laënnec wrote on emphysema: "The disease which I designate by this title is very little known, and has not hitherto been correctly described by any author. I, for a long time, thought it very uncommon, because I had observed only a few cases of it. But since I have made use of the stethoscope, I have verified its existence as well on the living, as on the dead subject, and am led to consider it as by no means infrequent. I consider many cases of asthma, usually deemed nervous, as depending on this cause. The chief reason of this affection having been so completely overlooked is that it is in some sort merely the exaggeration of the natural condition of the viscus".

Smoking was rare in this era, but it is a fact that emphysema may occur in non-smokers, particularly with a familial predisposition, or from environmental-provoking factors. Laënnec continued: "In opening the chest, it is not unusual to find that the lungs do not collapse, but they fill up the cavity completely on each side of the heart. When experienced, this will appear full of air. The bronchus of the trachea are often at the same time a good deal filled with mucous fluid". Thus, Laënnec had described a combination of emphysema and chronic bronchitis![4]

The term "chronic bronchitis" came into use in 1808, while the term COPD was first believed to have been used in 1965.[1,4] Previously, it was known by a number of different names, including chronic obstructive bronchopulmonary disease, chronic obstructive respiratory disease, chronic air flow obstruction, chronic air flow limitation, chronic obstructive lung disease, non-specific chronic pulmonary disease and diffuse obstructive pulmonary syndrome. The terms "chronic bronchitis" and "emphysema" were formally defined in 1959 at the CIBA guest symposium, and in 1962 at the American Thoracic Society Committee meeting on diagnostic standards.[6]

Definition

COPD is defined as follows by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), a project initiated by the National Heart, Lung and Blood Institute (NHLBI) and the World Health Organization (WHO):[7]

"COPD, a common preventable and treatable disease, is characterised by air flow limitation that is usually progressive, and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients".

"Chronic bronchitis" is defined as a chronic productive cough for three months in each of two successive years in a patient in whom other causes of chronic coughing, e.g. bronchiectasis, have been excluded.[8] It may precede or follow the development of air flow limitation.[9,10] This definition has been used in many studies, despite the arbitrarily selected symptom duration.

"Emphysema" is defined by the abnormal and permanent enlargement of the air spaces distal to the terminal bronchioles, which is accompanied by destruction of the air space walls, without obvious fibrosis.[11] The exclusion of obvious fibrosis was intended to distinguish the COPD disease, i.e. definition, clinical manifestations, diagnosis and staging alveolar destruction due to emphysema, from that due to interstitial pneumonia. However, increased collagen in the lungs of patients with mild COPD has been found in many studies, indicating that fibrosis can be a component of emphysema.[12,13]

While emphysema can exist in individuals who do not have air flow obstruction, it is more common in patients with moderate or severe air flow obstruction.[7,14]

Population and epidemiology

Worldwide, COPD affects roughly 329 million people, or nearly 5% of the population.[15] In 2013, it resulted in 2.9 million deaths, up from 2.4 million deaths in 1990.[7] The number of deaths is projected to increase owing to higher smoking rates and an ageing population in many countries.[8]

Globally, roughly 10% of people aged ≥ 40 years have air flow limitation, i.e. GOLD stage 2 or worse [forced expiratory volume in one second (FEV_1) ≤ 80% predicted], and up to 25% may have GOLD stage 1 (FEV_1 ≥ 80% predicted, but FEV_1/forced vital capacity ≤ 0.7). It is also suspected that up to 60–85% of people with COPD with mostly mild or moderate severity are undiagnosed.[16]

The disease affects men and women almost equally, as there has been increased tobacco use in women in the developed world. The global numbers are expected to continue to increase as risk factors remain common and the population continues to get older.[17]

COPD is considered to be the fourth leading cause of death worldwide. Mortality associated with COPD is rising, while that linked to cardiovascular disease is falling. COPD is expected to be the third leading cause of death in the next 15–20 years.[16]

Causes

Tobacco smoke is the primary cause of COPD, with occupational exposure and pollution from indoor fires being a significant contributing factor.[18] A number of industries and sources have been implicated, including high levels of dust in coal mining, gold mining and the cotton textile industry, occupations which involve cadmium and isocyanates, and fumes from welding.[19]

Working in agriculture is also a risk.[20] Typically, this exposure occurs over several decades before symptoms develop.[18]

A person's genetic make-up also affects the risk.[18] It is more common in relatives of those with COPD who smoke than in unrelated smokers.[3] Currently, the only clearly inherited risk factor is alpha-1 antitrypsin (AAT) deficiency. This risk is particularly high if someone deficient in AAT also smokes. AAT inhibits a wide variety of proteases. It protects tissue from the enzymes of inflammatory cells, especially neutrophil elastase. In its absence, i.e. in ATT deficiency, neutrophil elastase is free to break down elastin, which contributes to the elasticity of the lungs, resulting in respiratory complications such as emphysema or COPD in adults, and cirrhosis in adults or children.[21]

It is responsible for roughly 1–5% of cases, and the condition is present in 3–4 in 10 000 people.[21,22] Other genetic factors are being investigated, of which there are likely to be many.[20]

Acute exacerbations

Acute exacerbations of COPD, also known as acute exacerbations of chronic bronchitis, signify a sudden worsening of the COPD symptoms, i.e. shortness of breath, and the quantity and colour of the phlegm, which typically lasts for several days. It may be triggered by an infection with bacteria or viruses, or by environmental pollutants. At times, the cause or reason is simply not known. Improper use of medication can also lead to this.[23]

Infections appear to be the cause in 50–75% of cases,[23,24] with bacteria in 25% (including *Haemophilus influenzae, Streptococcus pneumoniae* and *Moraxella catarrhalis),* viruses in 25% (rhinovirus, coronavirus and parainfluenza), and both in 25%. Cold temperature may also play a role. Exacerbations occur more commonly in winter.[25]

Those with more severe underlying disease have more frequent exacerbations of 1.8 per year with mild disease, 2–3 per year with moderate disease, and 3.4 per year with severe disease. Those with many exacerbations have a faster rate of deterioration of their lung function.[26] Congestive heart failure and pulmonary emboli can worsen symptoms in those with pre-existing COPD.[27]

Pathophysiology

COPD is an obstructive lung disease in which chronic incompletely reversible poor air flow (air flow limitation) and the inability to breathe out fully (air trapping) exist.[27] This develops as a significant and chronic inflammatory response to inhaled irritants.[1] Chronic bacterial infections may also add to this inflammatory state.[26] The inflammatory cells involved include neutrophil granulocytes and macrophages. Those who smoke additionally have cytotoxic T lymphocyte involvement, and some patients with COPD have eosinophil involvement, similar to that in asthma.

COPD is characterised by both the destruction of lung parenchyma with loss of elastic recoil (causing emphysema), and infiltration of the walls of the small airways by inflammatory cells (causing chronic bronchiolitis or bronchitis. These two broad phenotypes are distinct entities, and they coexist and overlap in varying degrees in virtually everyone with COPD. The reasons for these variable phenotypes and their clinical importance are not that well understood.

Chronic poorly controlled COPD can lead to hypoxia, which occurs from poor gas exchange due to decreased ventilation from airway obstruction, hyperinflation and a reduced desire to breathe.[3] Airway inflammation is also increased during exacerbations, resulting in increased hyperinflation, reduced expiratory air flow and worsening of the gas transfer. This can also lead to insufficient ventilation, and eventually hypoxia. If present for a prolonged period, it can result in narrowing of the pulmonary arteries, while emphysema leads to the breakdown of capillaries in the lungs. Both these changes result in increased blood pressure in the pulmonary arteries, placing the patient at increased risk of developing *cor pulmonale.*[3]

Management

There is no known cure for COPD, but the symptoms are treatable, and its progression can be delayed. The major goals of management are to reduce the risk factors, manage stable COPD, prevent and treat acute exacerbations and manage associated illnesses.[28]

Other recommendations include an influenza vaccination once a year, a pneumococcal vaccination once every five years, and reduction in exposure to environmental air pollution.[27] Palliative care may reduce the symptoms in those with advanced disease. Supplemental oxygen has been shown to slow the progress of this disease. It has now been shown that giving morphine improves the feelings or sensations of shortness of breath. Noninvasive ventilation may be used to support breathing.[29]

Nonpharmacological

First and foremost, it is important to quit smoking. Keeping people from starting to smoke is a key aspect of preventing COPD. Stopping smoking in those who smoke is the only measure that has been shown to slow the progression of COPD.[30] Even at a late stage of the disease, it can reduce the rate of worsening lung function and delay the onset of disability and death. Stopping smoking decreases the risk of death by nearly 18%.[27]

Exercise

A programme with the aim of pulmonary rehabilitation should include coordinated aspects of exercise, disease management and counselling.[19] Pulmonary rehabilitation appears to improve overall quality of life and the ability to exercise, and reduce mortality in those who have experienced a recent exacerbation.[31] However, breathing exercises by themselves appear to play a limited role.[18] Some authors have shown that pursed lip breathing exercises may be useful.[16]

Lung volume reduction surgery

Consideration of lung volume reduction surgery is recommended in all patients with very severe COPD. The surgery provides a mortality reduction and improvement in quality of life,

especially in patients with upper lobe-predominant disease and poor exercise capacity or ability.[32]

Non-surgical, bronchoscopic lung volume reduction

Because of the morbidity and risk associated with lung volume reduction surgery, and its subsequent unpopularity, numerous companies and investigators have sought to produce a medical device that could be placed bronchoscopically, and which would reduce dead space ventilation, i.e. lung volume reduction surgery without the surgery. To date, none of these devices have worked effectively enough for their use to be recommended outside clinical trials. The most recent example was bronchoscopic lung volume reduction in the Exhale Airway Stents for Emphysema (EASE) trial, in which it was demonstrated that bronchoscopically placed airway stents with a one-way valve did not improve airway mechanics or dyspnoea.

Perhaps collateral ventilation or interalveolar air drift through the pores of Kohn are the most likely answers to this failure or ineffectiveness. These are miniscule anatomical intercommunications which allow air to fill back into emphysematous areas after air has been removed through the implanted device.[32]

Pharmacological

The GOLD guideline treatment table is the most well-known and accepted guideline for the treatment of COPD. It is summarised in Table 1.[16]

Bronchodilators

Inhaled bronchodilators are the primary medication used, and result in a small overall benefit.[4,33] There are two major types, β_2 agonists and anticholinergics. Both exist in long- and short-acting forms. They reduce shortness of breath, wheezing and exercise limitation, resulting in improved quality of life.[34] It is unclear whether or not they change the progression of the underlying disease.[27]

Long-acting bronchodilators (formoterol and salmeterol), and long-acting anticholinergics (tiotropium), have similar efficacy, including:

- An improvement in post-bronchodilator FEV_1, i.e. ~50–100 ml.
- An improvement in dyspnoea, i.e. ~3 points using the St George's respiratory questionnaire.
- A reduction in daily, short-acting beta agonist use by ~1 inhalation.
- The prevention of COPD exacerbations was better with tiotropium than salmeterol in one randomised trial, but the effect was quite small.[35]

Long-acting beta agonists (LABAs) have a cardiac effect, but have not been found to cause cardiovascular events, and don't have the very slightly increased risk of death associated with LABA monotherapy for asthma.

Tiotropium has been suspected of causing cardiovascular events based on observational trials, but the current consensus [based mainly on Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) randomised trial data and a meta-analysis] is that it does not cause cardiovascular events.[36]

Methylxanthines

The use of theophylline was summarised in a review carried out by Vaz Fragoso as follows. Theophylline may favourably affect the major factors associated with functional impairment in COPD, such as dyspnoea, exercise capacity, respiratory mechanics and respiratory muscle strength. Theophylline is generally considered to be a third-line bronchodilator drug in chronic COPD, after inhaled anticholinergics and beta 2 agonists.

Despite both smoking cessation and the use of inhaled bronchodilators, theophylline may reduce functional impairment and exacerbation frequency in patients with persistent functional impairment, but the effect in individual patients is variable. In general, patients with COPD can be adequately treated with serum levels in the 8–12 µg/ml range. Once an appropriate serum level has been achieved, subsequent measurements can be made at 6- to 12-month intervals, or if the patient's clinical status or concomitant medications change. When compared to acute intoxication, chronic theophylline overmedication is associated with a greater frequency of major toxicity, occurs at

Table 1: The Global Initiative for Chronic Obstructive Lung Disease guideline for the treatment of chronic obstructive pulmonary disease

Stage*	Mild (1)	Moderate (2)	Severe (3)	Very severe (4)
FEV_1/FVC	≤ 0.70	≤ 0.70	≤ 0.70	≤ 0.70
FEV_1	≥ 80% predicted	50–80% predicted	30–50% predicted	≤ 30% predicted, or ≤ 50% predicted with chronic respiratory failure
Treatment	Short-acting bronchodilator, as needed, for all patients with COPD			
		Consider pulmonary rehabilitation	Consider pulmonary rehabilitation	Consider pulmonary rehabilitation
		One or more long-acting bronchodilators	One or more long-acting bronchodilators	One or more long-acting bronchodilators
			Inhaled corticosteroid, if there are repeated exacerbations	Inhaled corticosteroid, if there are repeated exacerbations
				Long-term oxygen, if needed. Consider lung volume reduction surgery

* All patients should receive smoking cessation counselling and an influenza vaccination
COPD: chronic obstructive pulmonary disease, FVC: forced vital capacity, FEV_1: forced expiratory volume in one second

relatively lower theophylline levels, and cannot be predicted by the peak serum theophylline concentration.

Methylxanthines are not recommended for routine management in acute COPD exacerbations. In addition to a lack of efficacy in this setting, methylxanthines increase the likelihood of side-effects, e.g. nausea, vomiting and arrythmias.[37]

Corticosteroids

Corticosteroids are usually used in inhaled form, but may also be used orally to treat and prevent acute exacerbations. While inhaled corticosteroids have not shown benefit in people with mild COPD, they decrease acute exacerbations in those with either moderate or severe disease.[38]

Interestingly, in the Reduction in the Use of Corticosteroids in Exacerbated COPD (REDUCE) trial, it was demonstrated that a longer course of oral prednisone did not reduce the rate of repeat COPD exacerbations. Fifty-seven patients taking prednisone for 14 days had a repeat COPD exacerbation (37%), compared to 56 taking prednisone for 5 days (36%). Extra prednisone did not prolong the time to the next COPD exacerbation.[39] An important consequence of this was reduced corticosteroid exposure, and thus the side-effects.

When used in combination with a LABA, they decreased mortality more than either an inhaled corticosteroid or a LABA alone.[40] They have no effect by themselves on overall one-year mortality, and are associated with an increased rate of pneumonia.[41] It is unclear whether or not they affect the progression of the disease.[4] Long-term treatment with an oral glucocorticoidsteroid is associated with significant side-effects.[41]

Inhaled corticosteroid and LABA combination products cause pneumonia in a tiny proportion of patients. However, combination products may also reduce mortality slightly, based on the just barely negative Towards a Revolution in COPD Health (TORCH) trial. Inhaled corticosteroid/LABA combination products do not seem to cause increased risk of death from pneumonia. Even when inhaled, corticosteroids probably cause osteoporosis in a small number of susceptible patients.

The evidence is inconclusive as to whether any drug treatments for COPD modify (slow) the disease course or reduce mortality, but data from several clinical trials suggests that both inhaled corticosteroid/LABA combination products and tiotropium may lessen a decline in FEV_1 and slightly reduce mortality risk. In fact, better outcomes from "triple therapy", i.e. an inhaled corticosteroid, a long-acting beta-agonist and tiotropium given together, were suggested in an observational study on symptomatic patients with severe to very severe stable COPD.[42]

Treatment

Guidelines are available for the treatment of COPD exacerbations. They mainly recommend:

- Increasing the dose of short-acting bronchodilators, i.e. albuterol and/or ipratropium.
- Oxygen and ventilatory support for respiratory failure. A recent review showed that noninvasive positive pressure ventilation was likely to improve outcomes from COPD exacerbations.
- Considering theophylline for severe exacerbations.
- Adding oral corticosteroids, if bronchodilators are not successful.
- Treating most COPD exacerbations with 40 mg prednisone for five days, i.e. the 2014 GOLD guidelines. This was a significant change from the previous recommendation of 10–14 days. As discussed previously, five days of steroids was suggested as adequate treatment for COPD exacerbations in most patients in the REDUCE study.[43]
- Antibiotics are indicated in a patient with increased sputum production, purulent sputum, increased dyspnoea and an elevated white count, or who is febrile. [44]

The choice of antibiotics is also dependent upon the severity of the symptoms. "Simple" COPD generally refers to a person aged ≤ 65 years, with fewer than four exacerbations per year, minimal or moderate impairment in respiratory function and no co-morbid disease. Therapy in patients with "simple" COPD should target *H. influenzae, M. catarrhalis* and *S. pneumoniae,* and possibly pathogens of atypical pneumonia.The first-line treatment is a beta-lactam antibiotic, such as amoxicillin. The choice depends upon resistance patterns.

More complicated bronchitis occurs when the patient is aged ≥ 65 years, has four or more exacerbations per year, a FEV_1:FVC ratio of less than 50% on spirometry, has failed to respond to previous antibiotic treatment, and/or has co-morbidity. Treatment in these cases should target Gram-negative bacteria. The possibility of high antibiotic resistance should be considered. Sputum culture results are of great value in determining antibiotic resistance. The first-line treatment is cefuroxime or co-amoxiclav. Third-line treatment, as well as treatment in penicillin-allergic patients, is a fluoroquinolone, such as ciprofloxacin. An agent active against *S. pneumoniae* may have to be added.[45]

Replacing enzymes

AAT-deficient individuals who have, or show signs of developing, significant emphysema, can be augmented with a pooled, purified, human plasma protein concentrate replacement for the missing enzyme. Practitioners should immunise patients against hepatitis regardless.

Weekly intravenous infusions of AAT protein concentrates restore serum and alveolar AAT concentrations to protective levels.

It has not been proved in any controlled studies that intravenous augmentation therapy improves survival or slows the rate of emphysema progression. Results from the National Institutes of Health (NIH) patient registry and a comparison of Danish and German registries have been published, and both suggest that augmentation therapy has beneficial effects. Although they were not controlled treatment trials, the similarity of the results suggests that the findings are significant.

The NIH report described an overall death rate 1.5 times higher for those who did not receive augmentation therapy and a rate of FEV_1 decline (54 ml/year) in AAT-deficient individuals, roughly twice that of healthy non-smokers, but approximately 50% that of smokers (108 ml/year). Augmentation therapy did not improve the average FEV_1 decline (54 ml/year). However, participants with moderate air flow obstruction (FEV_1 35–60% of the predicted value) experienced a slower rate of decline, i.e. a mean difference of 27 ml/year).

Augmentation therapy is recommended in the current guidelines for individuals with abnormal AAT genotypes, who have AAT levels below 11 µm and documented evidence of air flow obstruction in pulmonary function tests.[46]

While firm guidelines have not been developed with respect to initiating or continuing augmentation therapy, most pulmonary physicians require the serum level to be below the threshold protective value, and the patient to have one or more of the following: signs of significant lung disease, such as chronic productive cough or unusual frequency of lower respiratory infection, air flow obstruction, accelerated decline of FEV_1, or chest radiographic or computed tomography evidence of emphysema.[46,47]

Some interesting developments

The role of the new phosphodiesterase-4 inhibitors (not properly discerned yet) has been the focus of relative recent new developments. Cochrane published an analysis on these new agents in 2011. Roflumilast, and its sibling, cilomilast, only improved post-bronchodilator FEV_1 by ~50 ml, and reduced exacerbation frequency by a relative 17%, in selected patients with GOLD stage 3–4 COPD who experienced coughing with sputum changes and had a history of exacerbations.

However, patients reported that these medications only provided a small effect on levels of breathlessness and quality of life. On the other hand, 5–10% of patients on trials who received roflumilast or cilomilast reported side-effects such as diarrhoea, nausea, vomiting and nasal congestion. There was also a two- to threefold increase in the risk of sleep or mood disturbance, although the total number of reported incidents was still small overall. There was no effect on rates of hospitalisation and deaths. Furthermore, because both exhibit anti-inflammatory effects, there were suggestions of an additive benefit on top of the inhaled corticosteroids, but the number of studies reporting this was small.[42]

Post-marketing data are essential to determine the new agents' real-world efficacy and risk of adverse events. Also, they have not yet been included in GOLD or other society treatment guidelines.

The role of long-term use of antibiotics

Macrolide antibiotics are increasingly recognised for their salutary anti-inflammatory effects in lung disease, potentially distinct from any antimicrobial effect.

It was noted by Albert *et al.* in a randomised trial that of 1 142 patients with severe COPD (FEV_1 ~40% predicted) who were randomised to take either azithromycin 250 mg or placebo daily for one year, those taking azithromycin experienced fewer exacerbations, described as follows:[47]

- There was a 27% reduction in exacerbations.
- There was a delay of 92 days in median time to the first exacerbation (174 vs. 266 days).
- According to the St George's respiratory questionnaire, quality of life improved by 2.8 points vs. 0.6 (with 4 being accepted as "clinically significant").

However, sadly, at least 32 more people in the azithromycin group experienced hearing loss (142 vs. 110), and hearing did not return to baseline on repeat testing in most.

Conclusion

COPD, whether chronic or acute, is a very distressing debilitating condition. Acute exacerbations can be partially prevented. Some infections can be averted by vaccination against pathogens such as influenza and *S. pneumoniae*. Regular medication use can prevent COPD exacerbations. LABAs, long-acting anticholinergics and inhaled corticosteroids ("triple-therapy") are now emerging as a very useful approach to managing COPD and reducing exacerbations. Important methods of prevention include smoking cessation; avoiding dust, passive smoking and other inhaled irritants; and yearly influenza and five-year pneumococcal vaccinations. Promising avenues for treating AAT deficiency exist.

Regular exercise, appropriate rest and healthy nutrition are advocated, as well as avoiding people who are currently infected with a cold or influenza, maintaining good fluid intake, and lastly, humidifying the home, in order to help reduce the formation of thick sputum and chest congestion.

References

1. Ziment I. History of the treatment of chronic bronchitis. Respiration. 1991;58 Suppl 1:37–42.
2. Pink puffer. The Free Dictionary by Farlex [homepage on the Internet]. c2016. Available from: http://medical-dictionary.thefreedictionary.com/pink+puffer
3. Emphysema. Vocabulary.com [homepage on the Internet]. c2016. Available from: https://www.vocabulary.com/dictionary/emphysema
4. Petty TL. The history of COPD. Int J Chron Obstruct Pulmon Dis. 2006;1(1):3–14.
5. Wright JL, Churg A. Pathologic features of chronic obstructive pulmonary disease: diagnostic criteria and differential diagnosis. Fishman's pulmonary diseases and disorders. 4th ed. In: Fishman A, Elias J, Fishman J, et al., editors. New York: McGraw-Hill, 2008; p. 693–705.
6. Weinberger SE. Principles of pulmonary medicine. 6th ed. Philadelphia: Elsevier Saunders, 2013.
7. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: updated 2015. GOLD [homepage on the Internet]. c2016. Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Apr2.pdf
8. Rennard S, Thomashow B, Crapo J, et al. Introducing the COPD foundation guide for diagnosis and management of COPD, recommendations of the COPD Foundation. COPD. 2013;10(3):378–389.
9. Celli BR, MacNee W, ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004;23(6):932–946.

10. Elbehairy AF, Raghavan N, Cheng S, et al. Physiologic characterization of the chronic bronchitis phenotype in GOLD grade IB COPD. Chest. 2015;147(5):1235–1245.
11. Rennard SI. COPD: overview of definitions, epidemiology, and factors influencing its development. Chest. 1998;113(4 Suppl):235S–241S.
12. Pierce JA, Hocott JB, Ebert RV. The collagen and elastin content of the lung in emphysema. Ann Intern Med. 1961;55:210–222.
13. Vlahovic G, Russell ML, Mercer RR, Crapo JD. Cellular and connective tissue changes in alveolar septal walls in emphysema. Am J Respir Crit Care Med. 1999;160(6):2086–2092.
14. McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. N Engl J Med. 2011;365(17):1567–1575.
15. Han MK, Agusti A, Calverley PM, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med. 2010;182(5):598–604.
16. Chronic obstructive pulmonary disease 2014 update (COPD Review, Lancet). PulmCCM [homepage on the Internet]. c2016. Available from: http://pulmccm.org/main/2012/review-articles/chronic-obstructive-pulmonary-disease-2012-update-copd-review-lancet/
17. World Health Organization. Chronic obstructive pulmonary disease (COPD) fact sheet No 315. Geneva: WHO, 2015.
18. Vestbo J. Definition and overview. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease, 2013.
19. National Heart Lung and Blood Institute. COPD. Treatment options. NHLBI [homepage on the Internet]. c2016. Available from: http://www.nhlbi.nih.gov/health/educational/copd/breathing-better/treatment-options.htm
20. Pirozzi C, Scholand MB. Smoking cessation and environmental hygiene. Med Clin North Am. 2012;96(4):849–867.
21. Foreman MG, Campos M, Celedón JC. Genes and chronic obstructive pulmonary disease. Med Clin North Am. 2012;96(4):699–711.
22. Lötvall J. Advances in combination therapy for asthma and COPD. Chichester: John Wiley & Sons, 2011.
23. Dhar R. Textbook of pulmonary and critical care medicine. New Delhi: Jaypee Brothers Medical Publishers, 2011.
24. Palange P. ERS handbook of respiratory medicine. Sheffield: European Respiratory Society, 2013.
25. Barnes P. Asthma and COPD: basic mechanisms and clinical management. 2nd ed. Amsterdam: Academic, 2009.
26. Beasley V, Joshi PV, Singanayagam A, et al. Lung microbiology and exacerbations in COPD. Int J Chron Obstruct Pulmon Dis. 2012;7:555–569.
27. Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. Lancet. 2012;379(9823):1341–1351.
28. Vestbo J. Introduction. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease, 2013.
29. Drummond MB, Dasenbrook EC, Pitz MW, et al. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA. 2008;300(20):2407–2416.
30. Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. [Cochrane review]. In: The Cochrane Library, Issue 1, 2006. Oxford: Update Software.
31. Puhan MA, Gimeno-Santos E, Scharplatz M, et al. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. [Cochrane review]. In: The Cochrane Library, Issue 10, 2011. Oxford: Update Software.
32. Shah PL, Slebos D-J, Cardoso PFG, et al. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomised, sham-controlled, multicentre trial. Science Direct [homepage on the Internet]. c2016. Available from: http://www.sciencedirect.com/science/article/pii/S0140673611610507
33. Van Dijk WD, van den Bemt L, van Weel C. Megatrials for bronchodilators in chronic obstructive pulmonary disease (COPD) treatment: time to reflect. J Am Board Fam Med. 2013;26(2):221–224.
34. Liesker JJ, Wijkstra PJ, Ten Hacken NH, et al. A systematic review of the effects of bronchodilators on exercise capacity in patients with COPD. Chest. 2002;121(2):597–608.
35. Volgelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. The New England Journal of Medicine [homepage on the Internet]. c2016. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1008378
36. Spiriva Respimat inhaler as safe as HaniHaler (TIOSPIR). PulmCCM [homepage on the Internet]. c2016. Available from: http://pulmccm.org/main/2013/randomized-controlled-trials/spiriva-respimat-european-inhaler-safe-handihaler-u-s-nejm/
37. Vaz Fragoso CA. Role of methylxanthines in the treatment of COPD. UpToDate [homepage on the Internet]. c2016. Available from: http://www.uptodate.com/contents/role-of-methylxanthines-in-the-treatment-of-copd
38. Gartlehner G, Hansen RA, Carson SS, Lohr KN. Efficacy and safety of inhaled corticosteroids in patients with COPD: a systematic review and meta-analysis of health outcomes. Ann Fam Med. 2006;4(3):253–262.
39. Cazzola M1, Andò F, Santus P, et al. A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD. Pulm Pharmacol Ther. 2007;20(5):556–561.
40. Shafazand S. "ACP Journal Club. Review: inhaled medications vary substantively in their effects on mortality in COPD". Ann. Intern. Med. 2013;158 (12): JC2.
41. Vestbo J. Therapeutic options. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease, 2013.
42. Chong J, Leung B, Poole P. In people with chronic obstructive pulmonary disease, what are the benefits and risks of phosphodiesterase 4 inhibitors? Cochrane [homepage on the Internet]. 2013. C2016. Available from: http://www.cochrane.org/CD002309/AIRWAYS_in-people-with-chronic-obstructive-pulmonary-disease-copd-what-are-the-benefits-and-risks-of-phosphodiesterase-4-inhibitors
43. Leuppi JD, Shuetz P, Bingisser R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. JAMA. 2013;309(21):2223–2231.
44. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007;176(6):532–555.
45. Wikipedia. Acute exacerbation of chronic obstructive pulmonary disease. Wikipedia [homepage on the Internet]. c2016. Available from: https://en.wikipedia.org/wiki/Acute_exacerbation_of_chronic_obstructive_pulmonary_disease
46. Campos MA, Lascano J. α1 antitrypsin deficiency: current best practice in testing and augmentation therapy. Ther Adv Respir Dis. 2014;8(5):150–161.
47. American Thoracic Society, European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003;168(7):818–900.
48. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med. 2011;365(8):689–698.