Emerging concepts and therapies for chronic obstructive pulmonary disease

Natya Raghavan, R. Andrew McIvor

Firestone Institute for Respiratory Health, Division of Respirology, McMaster University, Hamilton, Ontario, Canada

Correspondence to:
Natya Raghavan, MDCM, FRCPC,
Firestone Institute for Respiratory Health, Division of Respirology,
McMaster University, 237 Barton St. East, Hamilton, ON L8L 2X2, Canada,
phone: +1-905-521-2100,
fax: +1-905-577-8013,
e-mail: raghanat@hhsc.ca

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide. Although considerable advances have been made in the diagnosis and treatment of COPD, much remains to be done both to alleviate symptoms and reduce mortality associated with this condition. Previously, diagnosis, management, and research all centred on staging based on the forced expiratory flow in 1 second. It is now becoming apparent that this is inadequate to truly capture current disease burden and future deterioration. Fortunately, new approaches to care are constantly being identified. It is now known that symptoms and, in particular, exacerbations represent pivotal events in the patient’s life that should trigger optimization of care. Much work is currently underway to identify various phenotypes in COPD because it has become obvious that this is a heterogeneous disease and applying the same management algorithms for all patients is insufficient. Several new medications are at various stages of development, some being approved and on the market, while others are undergoing clinical trials. These allow for more options for individualized care of patients. In addition, new applications of old medications, such as long-term antibiotics, also provide new options for patients struggling with recurrent symptoms. Finally, the growing awareness that this is a heterogenous disease composed not only of differing phenotypes but also having significant extrapulmonary comorbidities have opened new avenues of research and interdisciplinary collaboration that will further enable us to offer personalized care to patients.

KEY WORDS
bronchodilators, chronic obstructive pulmonary disease, exacerbations, phenotypes, spirometry

Diagnosis and symptom identification

The cornerstone for the diagnosis of chronic obstructive pulmonary disease (COPD) remains evidence of air-flow obstruction on spirometry with the forced expiratory volume in 1 second (FEV₁) to forced vital capacity ratio of less than 70%. Patients with compatible symptoms require spirometry to confirm airway obstruction, and FEV₁ is still used as the marker of the grade of COPD to guide treatment.

The assessment, however, should not end there. A careful history of symptoms, such as dyspnea, cough, and sputum production, should also be included in the initial assessment. New tools such as the COPD assessment test (CAT) questionnaire have been shown to be useful in identifying the importance of a variety of symptoms in COPD and can be responsive to functional changes. It is a questionnaire that the patient can self-administer with 8 questions graded on a scale from 0 to 5, with a total score that can be monitored for changes over time. The CAT has been shown to deteriorate with exacerbations and is a tool that was developed to assess symptoms on a longitudinal basis. The components of CAT may even be helpful to identify those who have COPD in the general population.

Exacerbations are increasingly being identified as pivotal events in the disease course of a patient with COPD. The history of having an exacerbation is the single best predictor of having a subsequent exacerbation; thus, the history and frequency of exacerbations should be assessed at every visit. More recent data has looked at the long-term outcome of patients after suffering their first severe exacerbation requiring hospitalization. Suissa et al. investigated 73,106 patients during a 17-year follow-up. The risk of subsequent exacerbations rose 3-fold after the second serious exacerbation, and it seemed that the optimal time to intervene would be after the first exacerbation to prevent any subsequent exacerbations.
In addition, mortality after a severe exacerbation was at its peak in the week after admission at a rate of 40/10,000 patient-days. Interventions such as pulmonary rehabilitation, bronchodilators, inhaled corticosteroids (ICS) / long-acting β-agonists (LABA), and vaccinations have all been shown to be particularly effective in reducing exacerbations; thus, must be introduced early in patients who have had an exacerbation. An exacerbation may be the first opportunity to identify COPD in a patient who previously did not recognize symptoms. It is considered that those with early or mild disease tend to alter their daily routine, thus masking symptoms such as dyspnea that may already be present. They will thus not present for medical care until an event such as a respiratory illness is more severe or longer than expected. Once identified, these patients should have an expedited work-up to fully evaluate the extent of their disease and optimize management.

Phenotypes It has long been known that COPD is a heterogeneous disease. It is still unknown why despite the same history of smoke exposure one patient may develop crippling dyspnea while another remains well. Even the disease course and symptoms are heterogeneous. Current research is underway to identify the different phenotypes in COPD. Chronic bronchitis with a historical definition of cough and sputum on most days of the week for 3 months a year has been identified as a separate phenotype that responds differently to medications. The phosphodiesterase-4 inhibitor, roflumilast, has been shown to be effective in those with chronic bronchitis and a history of exacerbations, marking one of the first large drug trials to differentiate between subgroups with similar airflow obstruction based on history. The troublesome symptoms of chronic bronchitis respond poorly to other existing therapies; thus, more insight into the pathophysiology will hopefully identify new treatment targets.

Frequent exacerbations also seem to mark a separate phenotype that portends a worse prognosis. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines currently recommend the addition of an ICS to bronchodilator therapy in those with 2 or more exacerbations per year in addition to spirometric criteria of FEV1 less than 50%. This again highlights the importance of factors other than FEV1 in optimizing treatment and identifying phenotypes.

It has been noted for some time that the marker of sputum eosinophilia identifies a subgroup of those patients with COPD who respond to ICS. More recently, it has been shown that individuals with eosinophilic sputum are more likely to have an exacerbation when the ICS is withdrawn. The use of sputum indices is a noninvasive and rapid method of identifying phenotypes in COPD, which should become mainstream as the interest in individualized care continues.

Interest in identifying both phenotypes and genetic factors that predispose to symptoms of COPD has sparked the initiation of 2 large multicenter trials, ECLIPSE and COPD Gene, which are starting to provide new insight into the disease. They include assessments of baseline pulmonary function, health questionnaires, computed tomography imaging, biomarkers, and genetic analysis to allow better characterization of the phenotypes in COPD. These studies are ongoing and have begun to identify various genetic loci and biomarkers that may prove insightful in gene expression and thus in susceptibility and natural history of COPD. The longitudinal data have also demonstrated that changes in FEV1 are highly variable and are increased as expected in ongoing smokers but also in those with bronchodilator reversibility and emphysema.

Pharmacotherapy New long-acting bronchodilators Bronchodilators have long been the cornerstone of managing the symptoms of increased shortness of breath in COPD. The cumbersome era of short-acting bronchodilators that required multiple daily dosing has now given way to inhalers that can be taken once daily with equal or superior efficacy. Until recently, tiotropium, a long-acting antimuscarinic agent, was the only once-daily inhaler available. New studies have looked at these new long-acting agents in those with moderate-to-severe COPD based on the GOLD criteria.

Glycopyrronium bromide is a long-acting antimuscarinic dry-powder inhaler with a faster onset of action than tiotropium. The currently licensed dose is 50 μg once daily. Phase III studies have established improvement in dyspnea, quality of life, and reduced risk of exacerbation compared with placebo and results similar to that seen with tiotropium with a similar safety profile.

The bronchodilatory effect is seen on day 1 of administration; however, improvements in exercise endurance and quality of life are seen over time. Acldinium bromide is another long-acting antimuscarinic agent, which has also shown efficacy as a once-daily inhaler. In doses ranging from 100 to 400 μg once daily, it provided bronchodilation, improved symptoms, and decreased rescue inhaler use superior to placebo and similar to tiotropium and formoterol. Used twice daily, it seemed to provide greater relief of night-time symptoms than tiotropium taken once daily, but this finding still needs to be confirmed.

Indacaterol is a once-daily β-adrenergic agonist, which has shown bronchodilation similar to tiotropium in trials looking at dosages of 75 μg, 150 μg, and 300 μg. The currently approved dosage is 75 μg due to the fact that there was evidence of clinically important bronchodilation in the trials at 75 μg with no significant increase in bronchodilation at higher doses. This is the first once-daily β-agonist available and represents a new option for patients who either cannot tolerate an antimuscarinic agent due to side
Inhaled corticosteroids  ICS have revolutionized the management of asthma and, combined with a LABA in a single inhaler, they have additional benefits of gaining and maintaining asthma control along with a reduction in morbidity and mortality. Recent COPD guidelines have discouraged the use of ICS monotherapy but encouraged the use of ICS/LABA-combination inhalers.1

Although there was some suggestion from epidemiological studies of the benefit of monotherapy with ICS, when carefully studied no physiological or functional benefit in patients with advanced COPD was found even at high doses.23 However, this was further examined in large clinical trials designed to assess the benefit of ICS/LABA-combination inhalers vs. placebo and the individual components: ICS or LABA.

The TORCH trial compared salmeterol at a dose of 50 μg plus fluticasone propionate at a dose of 500 μg twice daily (combination regimen), administered with a single inhaler, with placebo, salmeterol alone, or fluticasone propionate alone for a period of 3 years. The primary outcome was death from any cause for the comparison between the combination regimen and placebo. This was a negative trial with a P-value of 0.052. However, much emphasis was placed on the benefit on secondary outcomes, which extended the previous observations of studies regarding the combinations of ICS and LABA in showing that the combination regimen reduced exacerbations significantly, as compared with placebo, including those exacerbations requiring hospitalization. The combination regimen was also significantly better than each of its components alone in preventing exacerbations, and these benefits were accompanied by sustained improvements in health status and FEV₁. However, the TORCH trial raised the controversial issue of pneumonia reported as an adverse event, which was higher among patients receiving medications containing fluticasone propionate (19.6% in the combination-therapy group and 18.3% in the fluticasone group) than in the placebo group (12.3%, P <0.001 for comparisons between these treatments and placebo).24

In a recent study, addition of a fluticasone furoate to vilanterol was associated with a decreased rate of moderate and severe exacerbations of COPD in patients with a history of exacerbation, but was also associated with an increased pneumonia risk. Pneumonia and fractures were reported more frequently with fluticasone furoate and vilanterol than with vilanterol alone. Eight deaths from pneumonia were noted in the fluticasone furoate/vilanterol groups compared with none in the vilanterol-only group.25

These benefits on secondary outcomes with ICS/LABA-combination inhalers compared to placebo or monotherapy with ICS do not remain so impressive when all patients are receiving foundation therapy with tiotropium alone.26 Although triple therapy, in which ICS and LABA are added to foundation therapy with tiotropium, is common in advanced disease, there is insufficient evidence to determine whether it is clinically superior to dual-bronchodilator therapy or combination therapy (ICS/LABA).27

Prophylactic antibiotics  With the understanding that exacerbations pose a great threat in the course of the disease, there has been increased interest in breaking the cycle of recurrent exacerbations. The idea that giving long-term antibiotics may decrease exacerbations was studied by Albert et al.28 in a large placebo-controlled trial of 1577 subjects randomized to daily azithromycin 250 mg or placebo for 1 year. They found a significant decrease in the number of exacerbations in this group of patients who had a history of at least 1 exacerbation requiring either emergency-room visit or hospitalization. Side effects included hearing loss in a small percentage of patients and although there was laboratory documentation of increased bacterial resistance, this did not cause any clinically significant treatment failure.28 Another group looked at 1 year of azithromycin given at a dose of 500 mg 3 times per week and also found a significant reduction in exacerbations; they included patients with a history of 4 or more exacerbations per year, further fine-tuning the selection of patients based on a higher risk of recurrent exacerbations.29 These studies provide evidence of benefit but the optimal duration of therapy is still unknown as there are potential risks of ongoing treatment beyond 1 year in this group of patients with multiple comorbidities.30

Potential targets  Research continues to better identify targets that can change the natural history of COPD. The identification of different phenotypes and better understanding of the pathophysiology will help further refine this process. Thus far, anti-inflammatory agents and mucolytics have been disappointing in clinical trials with either a lack of effectiveness or significant side effects, but the ongoing multicenter trials looking at genomics and biomarkers will hopefully identify new targets.31
Comorbidities and multidisciplinary care  Respiratory rehabilitation with its multidisciplinary approach has long been the cornerstone of optimal management in COPD. However, new data is showing the importance of medical comorbidities and their effect on symptoms, quality of life, and outcomes in COPD. The presence of anxiety and depression has long been linked to COPD; however, there is now evidence of increased mortality as well as decreased compliance with medications in COPD. Thus, collaboration with psychiatry and psychology and further study into the impact of interventions to treat the underlying depression may provide benefit in those with COPD and depression.32,33

COPD has also been identified as being associated with an increased incidence of cardiovascular disease, stroke, and diabetes mellitus. This association persisted even when adjusted for smoking status, which is a known risk factor for both COPD and atherosclerosis. The association was strongest for young patients given that all of these conditions increase in prevalence with age. This highlights the need of involving multidisciplinary teams in the care of these patients.34 There is a real concern that those labeled with COPD may have silent cardiac ischemia go undetected due to not working up other causes for shortness of breath.

Finally, debilitating dyspnea is still undertreated in end-stage COPD. Although guidelines recommend opioids in palliating dyspnea, there is still a hesitance among practitioners in using these agents. Recent work by Rocker et al.35 has shown that there is lack of connection between practitioners’ experience and comfort with opioids vs. patients’ experiences, which are positive in those who are carefully selected and titrated.35,36 Collaboration with palliative care should enhance treatment in this patient population. In fact, the updated GOLD guidelines recommend collaboration with palliative care both for inpatients and outpatients with COPD for enhanced symptom care. There is some evidence from the lung cancer population that involvement of palliative care teams may prolong survival, but this remains to be investigated in the COPD population.2

Conclusions  Although COPD remains a debilitating illness causing significant morbidity and mortality worldwide, recent progress gives us hope for enhanced care. The recognition of various phenotypes in the disease will hopefully allow us to better understand the natural history for individual patients whose trajectory varies. The understanding of the importance of a respiratory exacerbation has been highlighted and represents a time when patients should be identified to receive optimal and timely care with the hope of reducing future morbidity and mortality. New long-acting bronchodilators and combination bronchodilators provide promise of simplifying treatment regimens, and the increasing number of options will allow for more individualized selection of agents for patients. Antibiotics may have an enhanced role in preventing exacerbations although the full impact of this intervention has yet to be determined. Finally, the understanding of COPD as a complex, multi-organ inflammatory state should precipitate enhanced multidisciplinary teams to optimize both the underlying symptoms of COPD and comorbidities that have been associated with increased morbidity and mortality. As we understand more about the complex underpinnings of this disease, we will be able to provide more optimal care.

REFERENCES


ARTYKUŁ POGŁĄDOWY

Przewlekła obturacyjna choroba płuc – nowe koncepcje i terapie

Natya Raghavan, R. Andrew McIvor
Firestone Institute for Respiratory Health, Division of Respirology, McMaster University, Hamilton, Ontario, Kanada

SŁOWA KLUCZOWE
fenotypy, leki rozszerzające oskrzela, przewlekła obturacyjna choroba płuc, spirometria, zaostrzenia

STRESZCZENIE
Przewlekła obturacyjna choroba płuc (POChP) jest jedną z głównych przyczyn chorobowości i umieralności na świecie. Chociaż dokonał się znaczący postęp w rozpoznawaniu i leczeniu POChP, to wiele jeszcze pozostaje do zrobienia, aby całkowicie kontrolować objawy tej choroby oraz ograniczyć umieralność z jej powodu. Wcześniej rozpoznawanie, leczenie i badania naukowe koncentrowały się na ciężkości choroby określanej na podstawie FEV1. Obecnie staje się jasne, że takie podejście nie pozwala w pełni objąć bieżącego obciążenia związanego z chorobą ani jej progresji. Na szczęście ciągle pojawiają się nowe sposoby postępowania. Wiadomo, że dolegliwości, a szczególnie zaostrzenia choroby stanowią zasadnicze obciążenie dla chorego i powinny skłaniać do optymalizacji terapii. Trwają intensywne prace mające na celu zidentyfikowanie różnych fenotypów POChP; stało się bowiem oczywiste, że jest to choroba niejednorodna i stosowanie tych samych algorytmów postępowania dla wszystkich chorych nie jest wystarczające. Szereg nowych leków znajduje się na różnych etapach – niektóre zostały już zarejestrowane i wprowadzone do lecznictwa, inne zaś są oceniane w badaniach klinicznych. Daje to więcej możliwości indywidualizacji terapii. Ponadto nowe zastosowania już znanych leków, na przykład długotrwałe podawanie antybiotyku, również stwarzają nowe możliwości dla chorych z nawracającymi objawami. Wreszcie coraz większa świadomość tego, że POChP jest chorobą niejednorodną nie tylko z powodu różnych fenotypów, ale również z powodu współwystępowania istotnych chorób pozapłucnych, otworzyła nowe kierunki badań i współpracę interdyscyplinarną, które stworzą dodatkowe możliwości zindywidualizowanej opieki nad chorymi na POChP.