Update in Chronic Obstructive Pulmonary Disease 2018

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Chronic obstructive pulmonary disease (COPD) remains a leading cause of morbidity and mortality worldwide. In this Update, we review the progress made in 2018 on mechanisms of disease, clinical epidemiology, and therapeutic options and highlight areas for future research.

Mechanisms of Disease

Airway Biology and "Pre-COPD"

Reduction in ciliated cells and increase in mucin-producing cells are known features of COPD. Ghosh and colleagues demonstrated that compared with patients without COPD, those with COPD have fewer numbers and impaired self-renewal capacity of airway basal progenitor cells (1). The progenitor cell count correlated with lung function and the presence of progenitor cell depletion in some smokers without airflow obstruction suggest a possible "early" COPD phenotype (1, 2).

Lung Immunity and Infections

Individuals with COPD are prone to lung bacterial infections. Alveolar macrophages from patients with COPD show a selective defect in opsonic phagocytosis that is associated with bacterial colonization and FEV_1 (3, 4). In small airways, secretory IgA is an important component of mucosal defenses against infection. In mice exhibiting COPD-like features and lacking secretory IgA, neutrophil depletion, antibiotics, and roflumilast attenuated airway remodeling and emphysema (5, 6). These findings suggest that impaired immunity, infection, and neutrophilic inflammation may all contribute to COPD progression.

Other immune cell types are also involved in COPD pathogenesis. Finch and colleagues demonstrated increased cytotoxicity of lung natural killer cells in smokers with COPD compared with smokers without COPD, with the degree of cytotoxicity correlating with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage of disease severity (7). In a mouse model, natural killer cytotoxicity was largely independent of epithelial cell ligands and relied on priming by dendritic cells in an IL-15–dependent manner (7, 8).

Viral infections are a frequent cause of COPD exacerbations. In a murine elastase/LPS-induced emphysema model, the expression of IL-17 and IL-23 was increased after infection with the respiratory syncytial virus. Although this virus alone did not induce emphysematous changes in control animals, it potently exacerbated emphysematous changes present in elastase/LPS-treated mice. As administration of an anti–IL-17 antibody partially attenuated the effects of respiratory syncytial virus infection, it could be a future therapy for viral COPD exacerbations (9, 10).

Protease–Antiprotease Balance

Proteases and their regulators, such as AAT (alpha-1 antitrypsin), have garnered recent interest for their role in COPD pathogenesis. Polverino and colleagues reported that the expression of ADAM8 (ADAM metallopeptidase domain 8), a metalloproteinase, was higher in the airway epithelia of nonsmokers than in smokers without COPD and was further decreased in individuals with COPD (12). Similarly, cigarette smoke–exposed mice had decreased ADAM8 expression, and ADAM8 knockout mice developed more emphysema after cigarette smoke exposure than wild-type mice. ADAM8 induced epidermal growth factor receptor shedding from airway epithelial cells, leading to decreased mucin gene expression (11, 12). In contrast, Wang and colleagues reported higher ADAM9 expression in airway epithelia from patients with COPD than from nonsmokers and smokers without COPD (14). Furthermore, ADAM9 knockout mice exposed to cigarette smoke were protected from developing small airway fibrosis and emphysema (13, 14). These studies confirm that proteinases are significantly involved in the development of COPD.

One of the best-studied antiproteases is AAT, although its deficiency likely remains underdiagnosed in patients presenting with COPD. Although screening for AAT is available, some variants may be missed when relying on isoelectric focusing for diagnosis. Matamala and colleagues performed extended genotyping in patients with AAT deficiency and found seven novel variants of the *SERPINA1* gene that were not previously described (15). Most

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mutations led to intracellular accumulation of AAT polymers (15).

Cela1 is a stretch-activated digestive protease that may be important in stretch-dependent remodeling processes in the postnatal lung. AAT is an important regulator of this process, and Cela1 is increased in humans with AAT-deficient emphysema. Joshi and colleagues demonstrated that an antisense oligonucleotide mouse model of AAT deficiency resulted in emphysema with increased Cela1 mRNA (16). In addition, Cela1$^{-/-}$ mice were protected against emphysema in this model. These data support a potential role for anti-Cela1 therapies in AAT deficiency (16).

Another potential target for AAT deficiency was described by Nath and colleagues, who examined the activity of a major serine-threonine phosphatase, PP2A (protein phosphatase 2A), which was reduced in human bronchial epithelial cells from patients with COPD compared with nonsmokers (17). Expression of an endogenous PP2A inhibitor, CIP2A, and ERK (extracellular signal–related kinase) phosphorylation were increased in cells from patients with COPD. Silencing of CIP2A with a siRNA in human epithelial cells or treatment with erlotinib led to increased PP2A activity, decreased ERK phosphorylation, and a reduction in matrix metalloproteinases 1 and 9 (17, 18).

Genomics and Epigenomics

Although prior genome-wide association studies (GWASs) have identified variants associated with COPD, they do not explain most of the disease heritability. Prokopenko and colleagues conducted a large whole-genome sequencing study in subjects with severe COPD and identified more than 20 million new variants, 10,000 of which had potential importance on the basis of prior COPD GWAS regions (19).

Epigenetic modifications are potent regulators of gene transcription. Morrow and colleagues performed methylation quantitative trait loci analyses to look for SNPs associated with DNA methylation levels and integrated these data with GWASs and epigenome-wide association studies (20). The authors found significant colocalization of methylation quantitative trait loci and GWAS loci, thereby highlighting the importance of genetic–epigenetic interactions in COPD pathogenesis (20, 21). Epigenetic changes such as promoter hypermethylation may also contribute to neoplastic transformation. Leng and colleagues (23) examined sputum samples for the methylation status of 12 genes linked to lung cancer, COPD, and lung function decline and found significant associations between high methylation and FEV_1 decline, time to lung cancer incidence, and all-cause mortality (22, 23).

DNA Repair and Cell Cycle Regulation

Chronic tobacco use leads to the accumulation of DNA damage. Sears and colleagues described the role of xeroderma pigmentosum group C (XPC) DNA repair protein in smoking-related emphysema (24). XPC was uniquely downregulated among DNA repair genes in mice exposed to smoke, and XPC knockout mice exhibited airspace enlargement with age and smoke exposure. These findings may be related to the association between XPC deficiency and the activation of apoptosis and autophagy in lung epithelial cells (24).

Cigarette smoke may induce premature cellular senescence. Senescent cells can secrete proinflammatory mediators that may propagate an injurious pattern leading to COPD. Removal of the cyclin-dependent kinase inhibitor p16 delays cell senescence in mice. However, although cigarette smoke exposure in mice led to an upregulation of p16 in the lung, p16 knockout was not protective against emphysema despite some attenuation in acute inflammation. Therefore, chronic inflammation in COPD may progress in a p16-independent or senescence-independent manner (25, 26).

Lung Cancer and Immunotherapy

Tobacco use is the most important risk factor for the development of lung cancer. Mice exposed to cigarette smoke alternating with air on a monthly basis had a higher incidence and multiplicity of lung cancer as well as more severe emphysema than mice continuously exposed to the same cumulative amount of cigarette smoke. Therefore, intermittent exposure to cigarette smoke may be more harmful than continuous exposure. The mechanisms behind this thought-provoking observation remain poorly understood but could be related to the downregulation of nicotinic acetylcholine receptors or to the proliferation of cells that previously incurred smoke-induced DNA damage (27, 28).

Novel immune-based therapies have ushered in a new era in oncology. Mark and colleagues noted that lungs of patients with COPD had greater numbers of $CD3^+$, $CD4^+$, and $CD8^+$ cells as well as increased $CD4^+$ Th1 polarization compared with lungs of smokers without COPD (29). This finding was present both in the noncancerous lung tissue as well as in the matching cancer, suggesting that the immune composition of the lung permeates the tumor environment (29, 30). Further research is needed to clarify whether the Th1 differentiation in COPD-affected lung tissue is responsible for the observed improved outcomes after immunotherapy.

Pulmonary Hypertension

Pulmonary hypertension may develop in patients with COPD and portends a poor prognosis. MicroRNA (miRNA) dysregulation has been implicated in pulmonary hypertension pathogenesis. Musri and colleagues studied the miRNA expression profiles of pulmonary arteries from smokers with COPD, smokers without COPD, and nonsmoker control subjects, revealing differential regulation of multiple miRNAs (31). The miRNA miR-197 correlated with airflow obstruction and was downregulated in pulmonary artery vascular remodeling. Transcription factor E2F1, which is targeted by miR-197, was upregulated in pulmonary arteries of smokers versus nonsmokers, therefore tying together decreased miR-197 expression with cell cycle entry (31).

Clinical Manifestations

Environmental Factors

Environmental exposures including use of biomass fuels have long been recognized as potential risk factors for COPD. However, two recent well-conducted studies investigating this exposure revealed conflicting results. Although Siddharthan and colleagues confirmed increased odds of COPD with household air pollution exposure in their study of 13 low- and middle-income country settings (32), Amaral and colleagues found no such association in participants recruited from 25 sites of the Burden of Obstructive Lung Disease study (33). Likely contributors to this discrepancy include the cross-sectional nature of the studies and the self-reported use of biomass fuels (34). In another study

of World Trade Center–exposed firefighters, higher post-9/11 concentrations of blood neutrophils and eosinophils were independently associated with accelerated FEV_1 decline after 15 years (35), although it remains unclear whether disturbed blood leukocyte counts are markers of increased susceptibility to chronic airflow limitation or of impaired recovery potential after airway injury (36). Other environmental factors such as diet and place of residence have also been associated with COPD pathogenesis and outcomes. For example, a Western dietary pattern was linked to higher COPD prevalence, worse respiratory symptoms, and lower lung function (37, 38). In the SPIROMICS (Subpopulations and Intermediate Outcome Measures In COPD Study) cohort, a link was identified between rural residence and COPD exacerbations (39, 40).

Lung Function

Defining airflow obstruction as FEV_1/FVC ratio less than 0.7 versus the ratio below the lower limit of normal remains controversial. In an analysis of the TIOSPIR (Tiotropium Safety and Performance In Respimat) study, although the risk of all-cause mortality was similar between individuals with FEV_1/FVC greater than or equal to or less than the lower limit of normal, the latter group had a lower risk of cardiovascular events but a higher risk of respiratory exacerbations (41, 42).

The current use of FEV_1% predicted to grade the severity of airflow obstruction was further validated in a study that found it to be the best predictor of 5-year survival among four different categorization methods (43, 44). In a separate analysis comparing the 2015 to 2017 GOLD staging schema, the 2017 ABCD schema, which does not incorporate FEV_1, resulted in worse mortality risk prediction (45), highlighting the strong association between lung function and clinical outcomes in COPD. However, it should be emphasized that the main purpose of GOLD ABCD staging is to guide treatment and not to predict outcomes.

Several studies examining longitudinal lung function decline shed light on the multiple potential paths for disease progression. Ross and colleagues identified four distinct lung function trajectories in the Normative Aging Study, which they then applied to COPDGene (Genetic Epidemiology of COPD) participants (46, 47). The genetic contribution to these trajectories was as high as 83%, and membership in lower lung function trajectories was associated with greater parental histories of COPD, decreased exercise capacity, greater dyspnea, and more frequent COPD exacerbations. In the CARDIA (Coronary Artery Risk Development in Young Adults) study, the presence of any respiratory symptom in young adulthood (age 25 yr) was associated with excess FEV_1 and FVC decline and a higher incidence of obstructive and restrictive lung disease 30 years later (48, 49). In the COPDGene cohort, about a quarter of smokers with preserved ratio impaired spirometry transitioned to normal spirometry, whereas another quarter transitioned to GOLD 1 to 4 COPD over 5 years. Preserved ratio impaired spirometry was associated with lower mortality than COPD but higher mortality than those with normal spirometry (50, 51). Long-standing asthma is another potential pathway for COPD development. In a longitudinal study of women with prevalent asthma, nearly half developed COPD over more than 20 years of follow-up (52, 53).

Exacerbations

Prior exacerbations are a strong predictor of subsequent events. In a large study of patients with COPD, the number of moderate exacerbations during the first-year baseline period proportionately predicted the risk of subsequent moderate exacerbations and the risk of death over a mean follow-up of 4.9 years (54, 55). Comorbid conditions can also affect and be affected by exacerbation events. In one retrospective study of hospitalizations due to COPD exacerbations, obesity was associated with a longer length of stay and a higher use of noninvasive and invasive ventilation (56, 57). In the SUMMIT (Study to Understand Mortality and Morbidity in COPD) study of participants with COPD and increased cardiac risk, COPD exacerbations increased the risk of subsequent cardiovascular events, particularly in the first 30 days after exacerbation (hazard ratio, 3.8; 95% confidence interval [CI], 2.7–5.5) (58, 59).

In an analysis of the Nationwide Readmission Database, the incidence of 30-day readmissions after COPD exacerbations was 19.2%, with more than half attributed to respiratory conditions (60, 61). Factors associated with readmissions included lower income, higher comorbidity burden, longer length of stay, and discharge to a skilled nursing facility. In another study of Medicare beneficiaries, the incidence of readmission and death were 64.2% and 26.2%, respectively, 1 year after COPD exacerbation (62, 63). These findings underline the significant morbidity and mortality associated with exacerbations long after the immediate postdischarge period.

Imaging

Chest computed tomography (CT) contains a wealth of diagnostic and prognostic information. In a population-based cohort free of clinical lung disease, higher Pi10 (square root of wall area of a hypothetical airway with an internal perimeter of 10 mm), a measure of airway disease, was associated with faster lung function decline as well as increased incidence of respiratory-related hospitalization and death (64, 65). In a population-based study, total airway count was significantly lower in participants with mild to moderate COPD than in never-smokers and smokers without COPD and was independently associated with lung function decline (66, 67). Expiratory central airway collapse has been linked to significant respiratory morbidity in smokers. The presence of paraseptal emphysema in the paratracheal location has now been identified as a risk factor for expiratory central airway collapse (68, 69). A study from the SPIROMICS cohort showed that exposure to vapors, gas, dust, and fumes during the longest job held was associated with more severe emphysema and airway disease, even after accounting for smoking history (70, 71). A convolutional neural network analysis performed on chest CT scans from the COPDGene and ECLIPSE cohorts detected and staged COPD with good accuracy but showed fair discriminative ability to predict acute respiratory events and death (72, 73). More studies are needed to better understand the clinical potential of machine learning applications to chest imaging.

Comorbidities

Comorbidities are common in COPD and influence patient outcomes. A higher comorbidity burden as measured by the Charlson index was associated with increased readmission and death within 30 days of discharge for a COPD exacerbation (74). In SPIROMICS, comorbid anemia was strongly associated with decreased exertional capacity and worse health status (75). Osteoporosis is prevalent in COPD partially because of shared risk factors, such as smoking and steroid use. In a longitudinal study of current and former smokers, moderate to severe visually

assessed emphysema, but not FEV_1% predicted, was associated with accelerated decline of hip bone mineral density, thereby informing the selection of susceptible smokers for osteoporosis screening (76). Prevalence of anxiety symptoms among patients with COPD is also high. The Generalized Anxiety Disorder-7, Hospital Anxiety and Depression Scale, and Anxiety Inventory for Respiratory Disease questionnaires have fair to moderate psychometric properties in patients with COPD compared with a questionnaire based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria (77). Therefore, better screening tools for anxiety are still needed in COPD.

Therapy

Bronchoscopic Lung Volume Reduction

Bronchoscopic placement of valves results in improvement in lung function in both heterogeneous and homogeneous emphysema, as long as there are no interlobar collaterals (78, 79). In the LIBERATE (A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema) study, 190 subjects with heterogeneous emphysema were randomized to receive endobronchial valves versus standard of care (80). At 12 months, 47.7% in the intervention arm had an improvement in FEV_1 of at least 15%, compared with 16.8% in the control arm (80). Clinically meaningful improvements were also seen in quality of life, dyspnea, and the 6-minute-walk distance (Figure 1), thereby providing the evidence basis for Food and Drug Administration approval for use of this device in the United States.

High-Flow Oxygen Therapy

High-flow nasal cannula oxygen therapy has been shown to be beneficial in the acute setting of COPD exacerbations. In a randomized crossover trial of 32 participants with stable hypercapnic COPD, Nagata and colleagues showed that 6 weeks of therapy with high-flow nasal cannula for at least 4 hours per night during sleep at flow rates of 30 to 40 L/min in addition to long-term oxygen therapy reduced hypercapnia and resulted in improvements in respiratory quality of life (81, 82).

Exacerbations

Viral infections account for up to half of exacerbations (83). Stolz and colleagues tested whether treatment intensification at the onset of an upper respiratory tract infection, by doubling the dose of inhaled corticosteroid (ICS)/long-acting β-agonist (LABA) for 10 days in patients on low-dose ICS/LABA combination and at high risk for exacerbations, would reduce COPD exacerbations (84). In a double-blind, randomized, placebo-controlled study of 450 patients, they found no difference in exacerbation frequency in the subsequent 21 days between treatment arms, but intensification was associated with a 72% reduction in severe exacerbations requiring hospitalization.

Although theophylline is recommended as an additional choice for patients on ICS and recurrent exacerbations, the TWICS (Theophylline as Adjunct to Inhaled Corticosteroids on Exacerbations in Patients With COPD) study found that in 1,567 participants with high exacerbation risk and on ICS therapy, exacerbation frequency was similar in the low-dose theophylline and placebo groups (85). In a substudy of the SUMMIT trial that enrolled participants with COPD at increased cardiac risk, lung function, respiratory events, cardiac events, and all-cause mortality in those on LABAs were not affected by concurrent use of β-blockers (86, 87).

The role for "triple therapy" in COPD remains controversial. The IMPACT (Informing the Pathway of COPD Treatment) study randomized 10,355 patients to once-daily fluticasone furoate/umeclidinium/vilanterol (ICS/long-acting muscarinic antagonist [LAMA]/LABA) versus fluticasone furoate/vilanterol (ICS/LABA) versus umeclidinium/vilanterol (LAMA/LABA) over 52 weeks (88). The rate of moderate or severe exacerbations in the triple-therapy group was 15% lower than the ICS/LABA

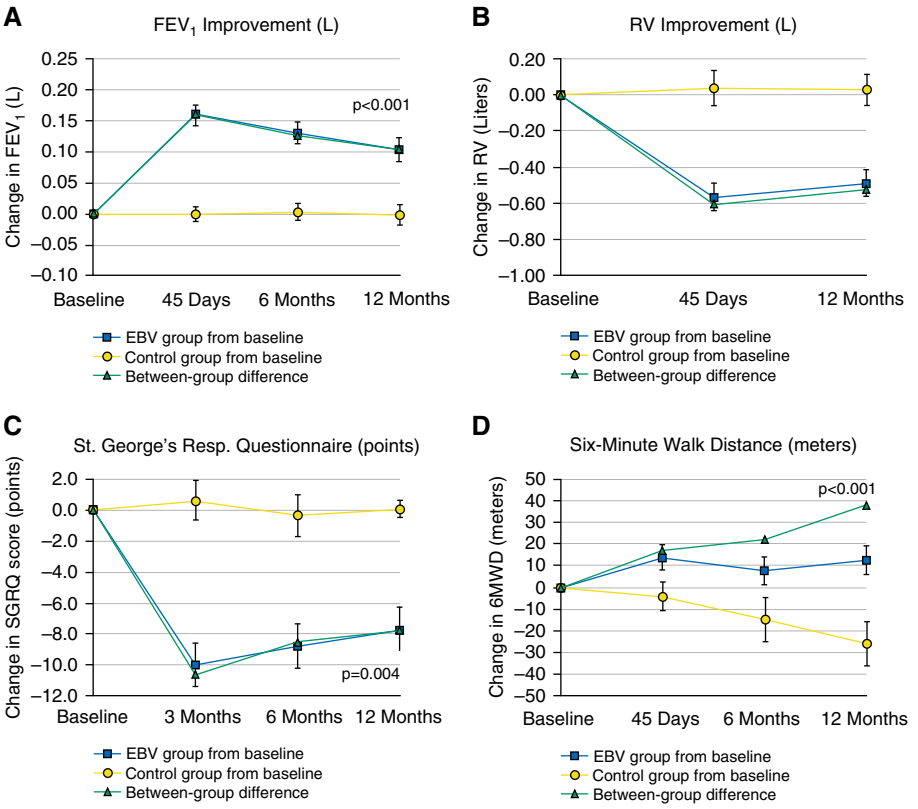

Figure 1. Data from LIBERATE (A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema) comparing valve-treated to placebo-treated patients demonstrating changes in clinical outcomes over time from baseline out to 12 months (80). Data presented are raw means ± SEM for changes from baseline to later time points after the bronchoscopy for Zephyr Endobronchial Valve (EBV) (blue squares), standard of care (yellow circles), and difference between EBV and standard of care (green triangles). (*A*) FEV_1. (*B*) Residual volume. (*C*) St. George's Respiratory Questionnaire. (*D*) Six-minute-walk distance. 6MWD = 6-minute-walk distance; Resp. = respiratory; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire.

group and 25% lower than the LAMA/LABA group. These differences were greatest in those with blood eosinophils greater than or equal to 150/μl. In the TRIBUTE (Extrafine Inhaled Triple Therapy versus Dual Bronchodilator Therapy in Chronic Obstructive Pulmonary Disease) study, participants with a history of exacerbations and randomized to the single-inhaler triple combination of beclomethasone diproprionate/formoterol fumarate/glycopyrronium experienced a lower rate of moderate to severe exacerbations over 1 year than participants randomized to the single-inhaler dual-bronchodilator combination of indacaterol/glycopyrronium (rate ratio, 0.848; 95% CI, 0.723–0.995) (89). The KRONOS (Triple Therapy with Budesonide/Glycopyrrolate/Formoterol Fumarate with Co-suspension Delivery Technology versus Dual Therapies in Chronic Obstructive Pulmonary Disease) trial also demonstrated that triple therapy improves lung function and symptoms and reduces COPD exacerbations compared with dual fixed-dose combination therapies of ICS/LABA and LAMA/LABA, but in a population not enriched for a history of exacerbations (90).

Given the risk of pneumonia with ICS therapy, there is growing recognition that it can be withdrawn when individuals no longer meet criteria for being on it (91). The SUNSET (Long-Term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease) trial showed that, in patients on triple therapy but without frequent exacerbations, a direct change from triple therapy to LAMA/LABA without tapering did not result in a meaningful decrease in lung function or in an increase in exacerbation frequency (92). However, there was a greater decrease in lung function and higher exacerbation risk in those with blood eosinophils greater than or equal to 300/μl, suggesting these patients are more likely to benefit from continued triple therapy.

More efforts are being made to develop new therapies and to identify patients likely to respond to specific therapies. A pooled analysis of two randomized trials (REACT [Roflumilast in the Prevention of COPD Exacerbations while Taking Appropriate Combination Treatment] and RE^{2}SPOND [Roflumilast Effect on Exacerbations in Patients on Dual (LABA/ICS) Therapy]) found that the benefit of adding the phosphodiesterase-4 inhibitor roflumilast to ICS/LABA in reducing exacerbation rates is greater in those with a history of prior hospitalization, two or more exacerbations in the prior year, and a higher eosinophil count (93, 94). Although there remains interest in the use of marijuana to treat chronic diseases, Abdallah and colleagues randomized 16 subjects with severe COPD to receive vaporized cannabis versus placebo and found no improvements in lung function, exertional breathlessness, or exercise endurance (95).

Lung Function Decline

Other than smoking cessation, oxygen therapy, and lung volume reduction procedures in a subset of patients, there are currently no disease-modifying therapies in COPD. Although *post hoc* and subgroup analyses of ICS/LABA and LAMA have shown some reduction in rate of FEV_1 decline, there are no studies that have primarily examined this issue. In a prespecified analysis of 15,457 participants in the SUMMIT study, Calverley and colleagues reported that the use of fluticasone furoate alone or in combination with vilanterol was associated with an 8 ml/yr lower decline in FEV_1 than placebo (96). Although these results are encouraging, it should be noted that the analysis was not performed on an intention-to-treat basis, and there were a considerable number of dropouts in the placebo arm (97).

Smoking Cessation

Melzer and colleagues demonstrated that the association between proactive smoking cessation interventions and prolonged quit rates was greater in those with chronic respiratory disease (odds ratio, 3.45; 95% CI, 1.59–7.47 vs. odds ratio, 1.34; 95% CI, 0.95–1.88) (98), suggesting that proactive measures to enhance tobacco quit rates are feasible and may be especially effective in smokers who have diagnosed COPD (99).

Disease Management

Early identification and treatment of exacerbations is likely associated with reduction in hospitalization rates. However, two multicenter randomized controlled studies examining the utility of telehealth monitoring for early detection of exacerbations failed to show any difference in hospitalizations over 9 to 12 months (100, 101). These data suggest that simply monitoring patients is neither medically effective nor cost effective (102).

Kalter-Leibovici and colleagues randomized 1,202 ambulatory patients with COPD to receive either recommended care or a disease management intervention (103). Disease management included trained COPD nurses delivering in-person and remote self-care education, monitoring symptoms and adherence to therapy, providing advice in the event of exacerbations, and coordinating care with other healthcare providers. There was no difference between the two groups in terms of first respiratory hospitalization or all-cause death. A similar trial, the AIR study, randomized 192 participants with moderate to severe COPD to receive health coaching by college graduates without any medical training versus usual care and showed mild improvement in quality of life and depression symptoms but no difference in COPD hospitalizations (104, 105).

Aboumatar and colleagues developed a self-care intervention with input from patients and caregivers to integrate transitional care support and chronic disease self-management (52). In a single-center study, 240 patients were randomized to receive usual transitional care or a 3-month individualized COPD self-management plan. Compared with usual care, the self-management plan was associated with a significant decline in COPD-related hospitalization and emergency department visits at 6 months and with improvements in the St. George's Respiratory Questionnaire score (52).

Physical Activity

It is now increasingly recognized that there is a disconnect between change in exercise capacity and daily physical activity in patients with COPD, as physiological improvements do not necessarily translate into increases in physical activity (106). Troosters and colleagues evaluated the relative impact of a self-management behavior-modification program combined with bronchodilator therapy and exercise training on exercise capacity and physical activity (107). They found that self-management behavior modification plus placebo was associated with a significantly increased step count at Week 12, but there were no further increases in step count with any of the other interventions (107). These data suggest that behavioral factors are important in increasing physical activity.

Coultas and colleagues performed a prespecified secondary analysis of the

COPD-SMART (Chronic Obstructive Pulmonary Disease Self-Management Activation Research Trial), which randomized 325 outpatients with stable COPD to usual care versus a home-based health coaching intervention delivered by telephone over 20 weeks (108). A greater proportion of participants in the health coaching arm reported being persistently active over the 18-month follow-up period (108, 109).

Patient Perspectives

In a comprehensive systematic review of 217 quantitative studies on outcomes valued by patients with COPD, symptom relief and exacerbations were rated as most important (110). These outcomes are currently recommended by GOLD to guide clinical management. Personalized medicine increasingly demands that patient experiences and preferences be taken into account to increase adherence (111). Results from the Patient Supplemental Oxygen Survey showed that more than 50% of patients on long-term oxygen therapy reported problems with oxygen use, including equipment malfunction, lack of physically manageable portable systems, and lack of high-flow portable systems (112). Improvements in the systems in place to support patients on oxygen therapy are still clearly needed.

Palliation

Gershon and colleagues conducted a population-based cross-sectional study using linked administrative data of 151,912 individuals with advanced COPD in Ontario between 2004 and 2014 (113). They found that the use of palliative care services increased 1% per year, from 5.3% in 2004 to 14.3% in 2014, whereas the use of long-term oxygen therapy increased 1.1% per year, from 26.4% in 2004 to 35.3% in 2013. The use of opioids remained stable. Although these data are encouraging, more efforts should be made to offer palliation to those with severe disease in the absence of disease-modifying therapies (114).

Future Perspectives

The progress made in 2018 in our understanding of the pathogenesis, progression, and management of COPD is encouraging. However, much work remains to fully elucidate the various clinical and biological phenotypes of this disease. Advances in the fields of systems biology, molecular profiling, and chest imaging hold promise for the ultimate quest of advancing personalized medicine in COPD. ■

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