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Chronic Obstructive Pulmonary Disease: A Worldwide Problem 671
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Respiratory diseases receive little attention and funding in comparison with other major causes of global morbidity and mortality. Chronic obstructive pulmonary disease (COPD) has been a major public health problem and will remain a challenge for clinicians within the twenty-first century. Worldwide, COPD is in the spotlight because of its high prevalence, morbidity, and mortality, and creates formidable challenges for health care systems. This review summarizes the magnitude of the COPD problem at the population and individual levels.

Pathobiologic Mechanisms of Chronic Obstructive Pulmonary Disease 681
Anthony Tam and Don D. Sin

The pathogenesis of chronic obstructive pulmonary disease (COPD) is not fully known. However, it is now well accepted that inflammatory responses to external triggers, such as cigarette smoke and biomass fuel, are important in COPD progression. Protease–antiprotease balance, autoimmunity, mucus hypersecretion, airway wall remodeling, and chronic respiratory infections have all been implicated in disease pathogenesis. This article reviews these and other pathways that have been associated with COPD.

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Marilyn G. Foreman, Michael Campos, and Juan C. Celedón

The marked variability in individual susceptibility to the detrimental effects of smoking on lung function and other findings suggest a significant genetic contribution to chronic obstructive pulmonary disease (COPD). The only known genetic risk factor for COPD, severe a1-antitrypsin (AAT) deficiency, explains only 1% to 2% of cases of this disease. Screening for severe AAT should be done in all cases of COPD. There is considerable interest in identifying susceptibility genes for COPD unrelated to severe AAT deficiency, as this could greatly enhance efforts to prevent, diagnose, and treat COPD by yielding novel insights into its pathogenesis.

Contribution of the Environment and Comorbidities to Chronic Obstructive Pulmonary Disease Phenotypes 713
Carlos H. Martinez and MeiLan K. Han

Chronic obstructive pulmonary disease (COPD) is characterized by significant disease heterogeneity. This heterogeneity suggests that various influences, including environmental and biological factors, probably contribute to the disease, but the validation of specific phenotypes has been problematic. This article reviews differences in the presentation and progression of
COPD in relation to environmental risk factors and comorbidities. The clustering of certain comorbidities in COPD could help to identify patients who share similar inflammatory pathways. New research covering large patient populations with extensive clinical and biological characterization, and advanced analytical methods can expand the potential to identify COPD phenotypes and develop targeted therapies.

The Role and Potential of Imaging in COPD

George R. Washko

Chronic obstructive pulmonary disease is a heterogeneous condition of the lungs and body. Techniques in chest imaging and quantitative image analysis provide novel in vivo insight into the disease and potentially examine divergent responses to therapy. This article reviews the strengths and limitations of the leading imaging techniques: computed tomography, magnetic resonance imaging, positron emission tomography, and optical coherence tomography. Following an explanation of the technique, each section details some of the useful information obtained with these examinations. Future clinical care and investigation will likely include some combination of these imaging modalities and more standard assessments of disease severity.

The Importance of the Assessment of Pulmonary Function in COPD

Kristina L. Bailey

Chronic obstructive pulmonary disease (COPD) is defined by airflow limitation caused by chronic bronchitis or emphysema. Spirometry is an essential step in the diagnosis and staging of COPD. Guidelines advise spirometry as the gold standard for COPD diagnosis. Spirometry is also an important part of monitoring COPD. Despite this, many patients are treated for presumed COPD without ever undergoing pulmonary function testing. This article reviews pulmonary function testing and the abnormalities seen in COPD. Discussed is the role spirometry plays in the diagnosis and management of COPD, and in quantifying the severity of COPD.

Role of Exercise in Testing and in Therapy of COPD

Miguel Divo and Victor Pinto-Plata

Dyspnea is the most frequent complaint limiting physical activities in patients with COPD and decreased exercise capacity is at the center of functional limitation of these patients. This article reviews several modalities of exercise testing, including the 6-minute walk test, stair-climbing test, shuttle walking tests, and cardiopulmonary exercise test. The article also highlights the relevance of the information provided and the impact of the results in a patient’s prognosis and suitability for treatment, including medical treatment, pulmonary rehabilitation, and lung volume reduction.

Defining Patient-Reported Outcomes in Chronic Obstructive Pulmonary Disease: The Patient-Centered Experience

Jonathan P. Singer and Roger D. Yusen

Chronic obstructive pulmonary disease (COPD) causes significant morbidity and mortality. Patients with COPD experience impaired health-related quality of life (HRQOL) and disability. However, many challenges exist in
the evolving field of HRQOL measurement and interpretation. This article defines HRQOL, discusses instruments used to measure HRQOL, and reviews related literature.

**COPD Exacerbations: Causes, Prevention, and Treatment** 789

Alex J. Mackay and John R. Hurst

The mechanisms of chronic obstructive pulmonary disease exacerbation are complex. Respiratory viruses (in particular rhinovirus) and bacteria play a major role in the cause of these events. A distinct group of patients seems susceptible to frequent exacerbations, irrespective of disease severity, and this phenotype is stable over time. Many current therapeutic strategies help reduce exacerbation frequency. Further work is required to develop novel anti-inflammatory therapies for exacerbation prevention and treatment. This article focuses on the cause of chronic obstructive pulmonary disease exacerbations, and the current preventative and acute interventions available.

**An Integrated Approach to the Medical Treatment of Chronic Obstructive Pulmonary Disease** 811

Sharon R. Rosenberg and Ravi Kalhan

Comprehensive medical care of individuals with chronic obstructive pulmonary disease (COPD) requires a detailed evaluation of patients beyond the measurement of lung function. Symptoms should be determined in an objective manner, particular attention should be paid to a history of exacerbations, and the presence of comorbid conditions should be determined. Exercise capacity determined by a 6-minute walk distance can also be informative. Virtually all COPD therapies improve respiratory symptoms, lessen exacerbation frequency, and improve quality of life; selection of COPD pharmacotherapy should be individualized to each patient’s symptom and exacerbation burden and their individual response to therapy over time.

**Medical Pneumoplasty, Surgical Resection, or Lung Transplant** 827

Francis C. Cordova

Bullectomy, lung volume reduction surgery and lung transplantation have been shown to improve lung function, exercise capacity and quality of life in patients with advanced COPD. Careful patient selection and the use of optimal surgical procedure are important to ensure good clinical outcome. Advances in bronchoscopic techniques have allowed non-surgical lung volume reduction that replicate the clinical benefit of LVRS without its’ associated morbidity and mortality. Promising endoscopic lung volume reduction techniques that are in various phases of development include the deployment of unidirectional endobronchial valves, instillation of biodegradable gel, and creation of airways bypass tracts.

**Smoking Cessation and Environmental Hygiene** 849

Cheryl Pirozzi and Mary Beth Scholand

Although there are nonmodifiable genetic risk factors for chronic obstructive pulmonary disease (COPD), most known risk factors for development
and progression of COPD can be corrected. Continued efforts to encourage smoking cessation and measures to reduce exposure to secondhand smoke, outdoor air pollution, biomass smoke, and occupational and related amateur exposures will have a significant impact on worldwide health.