Respiratory Care Year in Review 2010: Part 1. Asthma, COPD, Pulmonary Function Testing, Ventilator-Associated Pneumonia

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The purpose of this paper is to review the recent literature related to asthma, COPD, pulmonary function testing, and ventilator-associated pneumonia. Topics covered related to asthma include genetics and epigenetics; exposures; viruses; diet, obesity and exercise; exhaled nitric oxide; and drug therapy (β agonists, macrolides, tiotropium and monteleukast). Topics covered related to COPD include childhood disadvantage factors and COPD; vitamin D deficiency and COPD; β-blockers and COPD; corticosteroid therapy during COPD exacerbations; oxygen administration during

pre-hospital transport of patients with COPD exacerbation; and prognosis of patients admitted to the hospital for COPD exacerbation. Topics related to pulmonary function testing include methods and techniques; predicted values; natural history, pulmonary function in health and disease; and the COPD controversy. Finally, the paper includes the following topics related to ventilator-associated pneumonia: the tube, the intubation route, and the cuff; mechanical ventilation; the bundle; and cost. These topics were chosen and reviewed in a manner that is most likely to have interest to the readers of RESPIRATORY CARE. *Key words: asthma; β agonist; β blocker; COPD; corticosteroids; exhaled nitric oxide; oxygen therapy; pulmonary function testing; spirometry; ventilator-associated pneumonia; vitamin D.* [Respir Care 2011;56(4):488–502. © 2011 Daedalus Enterprises]

Introduction

There is an overwhelming volume of new literature relevant to respiratory care practice published each year. Faced with the time demands of work and family, it can be difficult to remain abreast of new evidence. It can be an even greater challenge to filter the literature to what is clinically relevant to one's practice and to update one's practice based on the most recent evidence. At the 56th International Respiratory Congress, members of the RESPIRATORY CARE editorial board presented a series of papers in the theme of "Year in Review." Topics were chosen that are likely to have special interest to the readers of RESPIRATORY CARE. We are pleased to publish these in 2 parts in the Journal. In this, Part 1, we cover asthma, COPD, pulmonary function testing, and ventilator-associated pneumonia.

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Asthma

Clinical care and research into asthma is progressing rapidly. For 2010, PubMed listed 4,854 publications related to asthma. Of these many publications, certain themes emerged that were areas of active investigation and discovery.

Genetics and Epigenetics

With the decoding of the human genome and development of single nucleotide polymorphisms, the ability to conduct genome-wide screening to identify susceptibility genes for complex diseases has become greatly enhanced. One of the more interesting findings relates to the gene HHIP, which has been identified as being associated with both asthma and COPD and is critical for lung development *in utero*. The Dutch hypothesis from 1961 suggested that a susceptible smoker was likely to be someone who has asthma or allergies in early life and then began smoking. Thus, there is a predisposition to developing COPD in later life. In the study by Weiss and colleagues, the HHIP gene was related to pulmonary function and changes in pulmonary function over time.[1] Pulmonary function tends to remain the same throughout life. So, if you are born with air flow limitation, you will probably spend your life with a similar degree of air flow limitation.

Many complex diseases like asthma are due to both genetic influences and to modification of gene expression that is potentially inheritable. These heritable modifications of DNA are called "epigenetic" and include DNA methylation, micro RNA, and modifications of histone acetylation. Histone modifications can mediate more rapid responses to environmental influences, and DNA methylation can silence gene expression over a long period of time. Environmental influences that can produce epigenetic changes include tobacco smoke (including *in utero* smoke exposure), polycyclic aromatic hydrocarbons, endotoxin, diesel exhaust particles, particulate matter, and allergens. These can be sampled by dendritic cells in the immature airway. These cells can then prime naive CD41 T cells to differentiate into allergic TH2 cells. Epigenetic

changes are now recognized as key mechanisms underlying the establishment and maintenance of the TH2 bias in asthma.[2]

Exposures

It has been shown that increased acetaminophen use in the first 2 years of life is associated with a significantly increased risk of childhood asthma.[3] This risk is less after adjusting for the frequency of respiratory infections. However *prenatal* exposure to acetaminophen predicted current wheeze in children at the age of 5 years and the risk of wheeze increased with increasing number of days of prenatal acetaminophen exposure.[4]

Chlorinated pools may influence airway responsiveness, as chlorine gas is irritating. It was shown that attendance at chlorinated pools before the age of 2 years was associated with an increased risk of bronchiolitis, and infant swimmers who developed bronchiolitis had a higher risk of asthma and respiratory allergies later in childhood.[5]

Environmental tobacco smoke is one of the strongest predictors of chronic respiratory illness in children, including the development of asthma. There are now data that show that *in utero* smoke exposure can increase airway responsiveness to methacholine among children with asthma. Moreover, intrauterine smoke exposure blunts the beneficial effects of inhaled corticosteroids (ICS) on airway hyper-responsiveness in children with asthma.[6]

One of the most interesting recent studies evaluated all hospital admissions for asthma in children under 15 years of age in Scotland, before and after a complete ban on smoking in public places was established in March 2006. Before this legislation, admissions for asthma were increasing at a mean rate of 5.2% per year, but after March 2006 there was a decrease in the rate of admissions of 18.2% per year. There was no interaction between hospital admission for asthma and age group, sex, urban or rural residence, or socioeconomic status.[7]

Viruses

Viruses are the most common precipitant of acute asthma in children. In North America, respiratory syncytial virus (RSV) bronchiolitis in the first year of life has been thought to be an asthma-like condition that can predispose to later asthma. Palivizumab (Synagis) is effective in preventing RSV disease in infants. Despite this, palivizumab given to preterm infants did not decrease the frequency of recurrent wheezing in children with a family history of atopy when compared to matched children who did not receive palivizumab.[8] It is still possible that RSV may predispose to recurrent wheezing, but in an atopy-independent mechanism.

A new group of human rhinoviruses, group C (HRVC), was recently identified. Asthma severity was assessed in a group of acutely ill children between the age of 2 and 16 on presentation to an emergency department, and respiratory viruses were identified in nasal aspirates. Over 85% of these children had moderate to severe asthma, and 99% were admitted to hospital. Human rhinoviruses (all groups) were detected in 87.5% of these children and other respiratory viruses in only 14.8%, most of whom also had rhinovirus. HRVC was present in 59.4% of these children and was associated with more severe asthma.[9]

Diet, Obesity and Exercise

In North America, obesity is epidemic among children and adults. Furthermore, asthma is more common in people with obesity, and asthma in the obese patient is more difficult to treat. Between 1995 and 2005, cross-sectional studies were performed in 29 centers in 20 countries on allergic disease and exposure factors for over 50,000 randomly selected school children. More frequent consumption of fruits, vegetables, and fish was associated with a lower lifetime prevalence of asthma, whereas high consumption of hamburgers was associated with higher lifetime asthma prevalence, but none of these foods were associated with allergic sensitization. Food selection according to the Mediterranean diet was associated with a lower prevalence of asthma ($P = .03$).[10]

A cross-sectional study of almost 18,000 school children under the age of 12 living in rural West Virginia showed that obese children were likely to be diagnosed with asthma, but regardless of their body mass index (BMI) percentile, children with asthma were more likely to have higher triglyceride levels and *acanthosis nigricans*.[11] In another large study looking at weight gain and asthma risk, BMI was measured in over 100,000 subjects born in the 1950s. The relative risk of asthma associated with a 3-unit increase in BMI was 1.14 in current smokers and 1.27 in never smokers, even after adjusting for confounders.[12] On the other hand, obesity has also been shown to be associated with asthma *misdiagnosis*. It has been reported in several studies that about 30% of adults are incorrectly diagnosed as having asthma.[13] In a study of almost 500 subjects with physician-diagnosed asthma, older subjects, men, and those with higher FEV_1 were more likely to have asthma misdiagnosed. But, more importantly, obese individuals who made urgent visits for respiratory symptoms were far more likely to receive a misdiagnosis of asthma (odds ratio 4.08). The authors also confirmed that obese people with asthma have lower lung function and more comorbidities compared with normal weight people with asthma.[14]

Vitamin D deficiency appears to be extremely common and associated with increased risk of cancer, heart disease,

and asthma. In 100 children assessed for 25-OH vitamin D levels, 47% had insufficient levels (< 30 ng/mL) and 17% were deficient with < 20 ng/mL. FEV_1 percent of predicted was positively correlated with vitamin D level ($P = .004$). Vitamin D deficiency was associated both with an increased risk of asthma and with steroid resistance.[15] Vitamin D may decrease the response to steroids. In adults with asthma, low vitamin D levels were associated with increased airway hyper-responsiveness and reduced response to ICS.[16]

Exercise can trigger asthma in some patients, and for that reason some children and adults with asthma have been cautioned against vigorous exercise. However, studies suggest that exercise is beneficial for asthmatics. After 3 months of an aerobic exercise training program, health-related quality of life significantly improved in subjects with asthma, compared with control asthmatics ($P < .001$) and the number of asthma-free days and anxiety and depression levels also significantly improved.[17] In ovalbumin-sensitized mice, a common model of asthma, aerobic exercise decreased total lung resistance by 60%, and, more interesting, exercise decreased airway smooth muscle thickness.[18]

Exhaled Nitric Oxide

Asthma monitoring using the concentration of exhaled nitric oxide (FeNO) has gained wider use in the last few years. FeNO and features of asthma were determined in 175 subjects with severe asthma enrolled in the National Heart Lung and Blood Institute Severe Asthma Research Program, and in 271 with non-severe asthma and 49 healthy subjects. FeNO levels were similar among subjects with severe and non-severe asthma, but subjects with high FeNO had greater airway reactivity to methacholine, more sputum eosinophils, more evidence of atopy, more hyperinflation, but significantly decreased awareness of their symptoms.[19] In a study of 29 subjects with severe refractory asthma compared with 27 with moderate asthma and 17 healthy controls, FeNO greater than 19 ppb identified those with predominantly eosinophilic asthma. FeNO was lower in subjects with neutrophils in their sputum, regardless of whether eosinophils were present.[20] Single breath (SB)-FeNO was measured in 44 children under the age of 2 years with recurrent wheezing. SB-FeNO was higher in infants with bronchodilator responsiveness ($P < .001$) and was associated with a lower $FEV_{0.5}$ measured by the chest compression technique. SB-FeNO was superior to lung function and bronchodilator responsiveness in predicting subsequent wheezing and steroid responsiveness.[21] In adults, the degree of FeNO elevation has been shown to be an independent predictor of asthma severity, and, among patients with severe asthma, identifies the most reactive asthma phenotype.[19]

FeNO has also been used to assess responsiveness to ICS. Subjects with suboptimal asthma control had a stepwise increase in treatment with maximal fluticasone-salmeterol for a month. Those who remained uncontrolled received oral corticosteroids for an additional month. With this approach, 53/102 subjects or 52% gained control. Those who achieved control were more likely to have positive skin prick tests for allergies, positive bronchodilator response, and FeNO > 30 ppb. FeNO had a sensitivity of 87.5% and a specificity of 90.6% in identifying the steroid responsive asthmatics.[22]

Drug Therapy: β Agonists, Macrolides, Tiotropium, and Monteleukast

The use of long-acting β agonists (LABA) as monotherapy has been associated with increased risk of asthma death, but there are few data evaluating if steroids attenuate this risk. A meta-analysis was conducted of asthma-related deaths in randomized controlled clinical trials from the GlaxoSmithKline database comparing salmeterol with non-LABA treatment in asthma. Two large studies (SMART and SNS) contributed 86% of the asthma deaths. Salmeterol monotherapy was shown to significantly increase the risk of asthma mortality but there was no evidence that the combination of salmeterol and fluticasone was associated with an increased risk.[23]

In 2010, 2 studies of intravenous monteleukast as adjunctive therapy for acute asthma reported conflicting results. In children, a randomized controlled trial in acute asthma showed intravenous monteleukast to have no effect on pulmonary function, symptoms, or clinical course.[24] In contrast, in a study of 583 adults with acute asthma treated with 7 mg of intravenous monteleukast or placebo, the intravenous monteleukast group had a small but significant increase in pulmonary function. However, this did not change the frequency of admission to hospital or long-term outcome.[25]

Ipratropium bromide has been used for the treatment of acute asthma and has been shown to be synergistic with β agonists. There have been few studies on anticholinergic therapy for asthma outside of the emergency department. A 3-way randomized crossover trial in 210 adult subjects with inadequately controlled asthma evaluated the addition of tiotropium bromide to ICS compared with doubling the ICS dose or adding a LABA. The use of tiotropium was superior to a doubling dose of ICS as assessed by morning peak flow, the proportion of asthma control days, pulmonary function (the improvement was also greater than adding a LABA), and symptom scores.[26]

Statin drugs have also been shown to be anti-inflammatory. A study was undertaken in 51 subjects with asthma and sputum eosinophils to determine if adding simvastatin would improve asthma control. There was no significant

difference in the ICS dose required to achieve control between subjects receiving simvastatin and placebo.[27]

Macrolide antibiotics also have been shown to have immunomodulatory effects, and there have been several studies suggesting benefit in using low dose macrolides for treating asthma. A study population of 92 adults with asthma entered into a randomized trial to evaluate the effect of 16 weeks of clarithromycin added to an ICS therapy. Clarithromycin was shown to improve bronchial hyper-responsiveness, increasing the PC20 methacholine by 1.2 ± 0.5 doubling doses ($P = .02$).[28]

A very important study evaluated step-up therapy in 182 children, 6–17 years of age, who had uncontrolled asthma despite receiving 100 μg twice daily of fluticasone aerosol. Children were randomly assigned to receive a higher dose of twice daily fluticasone (250 μg), 100 μg fluticasone with an addition of 50 μg of LABA twice daily, or 100 μg fluticasone twice daily plus 5 or 10 mg of a leukotriene receptor antagonist (LRTA) once daily. A triple crossover design was used and a composite of asthma exacerbations, control days, and FEV_1 was used to determine if there was a differential response. A differential response occurred in 161 of the 165 subjects. The response to LABA step up was most likely to be the best response, but this was highly variable and many children had a best response to ICS or LTRA step up. Hispanic and non-Hispanic white children were more likely to have a best response to LABA step up therapy, and black children were equally likely to have the best response to LABA or ICS step up. Children who did not have eczema were most likely to have the best response to LABA step up ($P = .006$).[29]

Other Studies

Asthma is associated not only with bronchial hyperresponsiveness but also with mucus retention. Ciliary beat frequency and beat pattern were measured in epithelial strips from 7 subjects with mild, 7 with moderate, 19 with severe asthma, and 9 controls. Ciliary beat frequency was decreased in moderate and severe asthma compared to controls ($P < .01$), and dyskinesia and motility indexes were highest in severe asthma. Abnormalities were strongly related to the severity of disease ($P < .001$). This could be one reason for poor mucus clearance in patients with asthma.[30]

One of the more unusual and exciting studies from 2010 evaluated the presence of bitter taste receptors in the airway. Bitter taste receptors on the tongue evolved to evoke signals to avoid ingesting certain plant toxins. The bitter receptors, TAS2R, were also found on human airway smooth muscle, and bitter agonists such as chloroquine and denatonium increased intracellular calcium in airway smooth muscle in a receptor dependent manner. Normally, this would be expected to evoke muscle contraction, but, paradoxically, the bitter tastants caused relation in the smooth muscle and dilatation of airways that was 3 times greater than that elicited by a β adrenergic receptor agonist![31] This suggests a potentially novel treatment for asthma.

COPD

COPD affects an estimated 24 million adults and is the fourth leading cause of death in the United States.[32] A growing body of literature attests to the importance of this disease as a leading public health problem.

Childhood Disadvantage Factors and COPD

Epidemiological studies in adults have established the relationship of smoking, occupational exposures, exposure to biomass fuels, and respiratory infections with development of COPD.[32] There has been lesser emphasis on the influence of lung development in childhood on subsequent occurrence of COPD later in life.[33]

Svanes et al[34] analyzed data from the European Community Respiratory Health Survey (ECRHS) that included a multicultural population with wide variations in prevalence of COPD. Standardized spirometric measurements as well as extensive interview data were obtained. ECRHS I was conducted at 29 centers from 1991 to 1993, and included 13,359 adults ages 20–44 years. A follow-up survey (ECRHS II) was conducted at 28 centers from 1998 to 2002, with a mean follow-up of 8.9 years. This survey included 7,738 subjects (ie, 58% of the original cohort). The investigators performed a cross-sectional analysis of lung function and COPD, using data from both ECRHS I and ECRHS II. They also performed a longitudinal analysis of lung function decline for subjects with lung function data in both ECRHS I and ECRHS II. Five childhood disadvantage factors were identified to significantly ($P < .001$) influence adult FEV_1 after adjusting for smoking, education, social class, height, age, and center. These childhood disadvantage factors included (1) a history of maternal asthma, (2) paternal asthma, (3) asthma in childhood, (4) severe respiratory tract infection below 5 years of age, and (5) maternal smoking. The diagnosis of asthma as a child carried the strongest risk, with 10-fold higher risk of stage 2 COPD in men and 4-fold higher risk of stage 2 COPD in women. In comparison to smoking, the childhood disadvantage factors were equally prevalent in the general population, had an equally large impact on lung function and development of COPD, with a slightly smaller impact on lung function decline.

The importance of recognizing these childhood disease factors is that prevention programs for COPD could be initiated at a much younger age than is currently practiced.

Respiratory therapists could play an especially important role in providing education about maternal smoking during pregnancy and the perinatal period, and to increase the focus on early detection and treatment of childhood asthma. Other prevention efforts should aim to increase vaccination rates against common lower respiratory tract infections and provide closer follow-up for subjects with childhood disease factors.

Vitamin D Deficiency and COPD

Vitamin D deficiency is well known to accelerate osteopenia and osteoporosis. In recent years, vitamin D deficiency has also been correlated with a higher prevalence of cancers, autoimmune disease, infections, and cardiovascular diseases.[35] There is an unexpectedly high prevalence of vitamin D deficiency among the elderly population in the United States and Europe, with an estimated 40–70% of this population having low circulating levels of 25-hydroxyvitamin D (25-OHD, levels below 20 ng/mL or 50 nmol/L).[36-38] In healthy subjects included in the National Health and Nutrition Examination Survey (NHANES III), 25-OHD levels were found to significantly correlate with FEV_1 and forced vital capacity (FVC).[38]

Janssens et al[39] included 414 individuals who were not taking vitamin D supplements, > 50 years of age, with a history of smoking > 15 pack-years. Unlike previous investigators, they compared patients with COPD versus a group matched for age, sex, and smoking history but without COPD. In patients with COPD, they found a significant correlation between 25-OHD levels and FEV_1. A higher proportion of patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 3 or 4 COPD had low 25-OHD levels compared to smokers with normal lung function ($P < .001$). The investigators also determined the effects of variants in the rs7041 and rs4588 vitamin D binding genes on 25-OHD levels. Among homozygous carriers of the rs7041 at risk T allele, 25% of patients had low 25-OHD levels. Logistic regression analysis with adjustment for age, sex, and smoking history revealed that homozygous carriers of the rs7041 T allele had an increased risk of COPD (odds ratio 2.11, 95% CI 1.20–3.71).

Both environmental and genetic factors probably contribute to development of vitamin D deficiency in patients with COPD. Because of the high prevalence of vitamin D deficiency in patients with severe or very severe COPD, supplementation with vitamin D should be considered for this group of patients.

β-Blockers and COPD

Cardiovascular diseases are common in patients with COPD and account for most deaths in these patients.[40,41] β-blockers are highly efficacious for treatment of congestive heart failure and ischemic heart disease and can significantly reduce mortality due to these disorders.[42,43] Physicians avoid using β-blockers in patients with COPD and concurrent cardiovascular disease because of concerns about adverse pulmonary effects and their effect on response to β-agonist bronchodilators.[44]

Rutten et al[45] questioned whether long-term β-blocker use improves survival and reduces risk of exacerbations in patients with COPD. This observational cohort study was conducted in the Netherlands, where all residents, except nursing home residents, are registered with a general practitioner. The investigators employed a network electronic database from 35 general practitioners in 23 practices. Data from January 1995 to December 2005 were screened for patients with a diagnosis of COPD. The study group comprised 2,230 patients with a mean age of 64.8 years. β-blockers were prescribed in 29.8% of the patients, and the majority (24.4%) received cardio-selective β-blockers. During a mean follow-up period of 7.2 years, 30.8% of the patients died: 27.2% of those who used a β-blocker, compared with 32.3% of those who did not use a β-blocker ($P = .02$). At least one exacerbation occurred in 47.3% of the patients; 42.7% of those using a β-blocker and 49.3% of those who did not ($P = .005$). The crude and adjusted hazard ratios with Cox regression analysis of β-blocker use for mortality were 0.70 (95% CI 0.59–0.84) and 0.68 (95% CI 0.56–0.83), respectively, whereas the crude and adjusted hazard ratios for exacerbation of COPD were 0.73 (95% CI 0.63–0.83) and 0.71 (95% CI 0.60–0.83), respectively.

Thus, long-term β-blocker use, especially with cardioselective β-blockers, may improve survival and decrease risk of COPD exacerbation in patients with COPD. The concurrent administration of inhaled medications does not interfere with results of β-blocker use. If indicated, cardioselective β-blockers should be prescribed in patients with COPD. A randomized controlled trial is needed to address this important observation.

Corticosteroid Therapy During COPD Exacerbations

Corticosteroid therapy during COPD exacerbation improves lung function, reduces the risk of treatment failure, and reduces hospital stay.[46,47] Guidelines by experts in the United States, United Kingdom, and Europe recommend low doses of corticosteroids given orally for treatment of COPD exacerbation.[48-50]

Lindenauer et al[51] performed a retrospective cohort study from a database of 414 hospitals in the United States, mainly small to medium non-teaching hospitals, serving a largely urban population. Patients admitted between January 2006 and December 2007 who were > 40 years old and had a principal diagnosis of COPD exacerbation or

acute respiratory failure with a secondary diagnosis of COPD with exacerbation of emphysema were included in the analysis. Those patients who were treated with systemic corticosteroids during the first 2 hospital days were analyzed even if the dose and route of administration were later changed during the hospital course. The primary outcome was a composite measurement of treatment failure that included initiation of mechanical ventilation after the 2nd hospital day, death in hospital, or readmission for COPD exacerbation within 30 days of discharge.

The study included 79,895 patients, with a median age of 69 years. Initial high dose corticosteroid therapy was instituted in 73,765 patients (92%), median 600 mg, IQR 350–781 mg, whereas initial low dose corticosteroid therapy was instituted in only 6,220 patients (8%), with a median dose of 60 mg, IQR 40–120 mg. The therapy was switched from initial low dose to high dose therapy in 1,356 patients (22%). There were differences between the groups receiving high dose versus low dose corticosteroids in terms of age, race, insurance status, region, comorbidities, and other therapies employed during hospital stay. The composite end point of treatment failure occurred in 10.9% of patients receiving high dose and 10.3% of patients receiving low dose corticosteroids. Further analysis of the data to adjust for a propensity matched cohort and balanced covariates to correct for remaining differences between the groups showed a slightly lower risk of treatment failure, shorter hospital stay, and lower hospital costs in the group receiving low dose corticosteroids. Lower doses of oral corticosteroids should be preferred for patients admitted to the hospital for COPD exacerbation, provided they are not admitted to an intensive care unit (ICU).

Oxygen Administration During Pre-hospital Transport of Patients With COPD Exacerbation

The pre-hospital transport of patients with COPD exacerbation includes nebulized bronchodilators (most powered with O_2), oxygen, and corticosteroids. Administration of oxygen treats hypoxemia, but is often associated with development or worsening of hypercapnia.[52,53]

Recent audits of patients admitted to the hospital for COPD exacerbation have shown that administration of high flow oxygen is associated with increased mortality, longer hospital stay, need for mechanical ventilation, and admission to high dependence units.[54,55] In contrast, the use of titrated oxygen treatment for in-hospital patients with COPD exacerbation is associated with lesser acidosis, a lower requirement for mechanical ventilation, and reduced mortality.[56]

Austin et al[57] conducted a randomized controlled trial to determine if routine administration of high oxygen concentrations in the pre-hospital setting to patients with COPD exacerbation is associated with increased mortality. In this trial, paramedics (*not* patients) were randomized. The trial was conducted between June 2006 and July 2007, and 405 patients with presumed COPD were transported by ambulance. Among this group, the diagnosis of COPD was confirmed by pulmonary function tests in 214 patients. High flow oxygen was administered via non-rebreathing mask at 8–10 L/min, and the nebulizer was driven by O_2 at 6–8 L/min. Low flow oxygen was administered via nasal cannula and titrated to an S_{pO_2} of 88–92%, via pulse oximetry. In this latter group, the nebulizer was powered by air, and aerosol was delivered via mask. Patients also received standard therapy for COPD exacerbation. All deaths occurred after arrival to the hospital. Respiratory failure was the primary cause of death, and most (70%) deaths occurred within 5 days of admission. The mortality rate was 9% in patients who received high flow oxygen and 4% in those who received low flow oxygen. In the subgroup of patients with confirmed COPD, mortality was 9% in those who received high flow oxygen and 2% in those who received low flow oxygen. Compared to the high flow arm, the use of low flow oxygen reduced mortality by 58% in all patients (relative risk 0.42, 95% CI 0.20–0.89, $P = .02$), and by 78% in the group with confirmed COPD (relative risk 0.22, 95% CI 0.05–0.91, $P = .04$).

Thus, uncontrolled oxygen therapy during pre-hospital transport may be detrimental in patients with COPD exacerbation, with the number needed to harm of 14. In the pre-hospital setting, uncontrolled oxygen therapy should be avoided, and oxygen should be titrated to achieve an S_{pO_2} of 88–92%.

Prognosis of Patients Admitted to the Hospital for COPD Exacerbation

Within the past 10–15 years, several guidelines have been published in an effort to improve the prognosis of patients with COPD. In a prospective cohort study, Almagro et al[58] determined whether long-term mortality after discharge from a hospitalization related to COPD had improved in recent years. The authors studied 2 cohorts 7 years apart (135 participants enrolled from November 1996 to May 1997, and 181 participants enrolled from June 2003 to September 2004). All consecutive patients admitted for COPD exacerbation at one hospital were included, and their comorbidities and treatments were assessed, with follow-up for up to 3 years after discharge. The patients had at least moderate COPD, measured via spirometry. The cohorts were comparable in baseline age, sex, comorbidities, functional status, number of hospitalizations, and COPD exacerbations in the previous year. The 3-year mor-

tality was lower in the 2003–2004 cohort than in the 1996–1997 cohort (38.7% vs 47.4%, respectively, $P = .02$). The relative risk of death after adjustment for age, body mass index, comorbidities, lung function, and modified Medical Research Council dyspnea scale was 0.66 (95% CI 0.45–0.97). This improvement in prognosis of patients admitted to the hospital for COPD exacerbation is probably due to standardized COPD management, better management of comorbidities, and possibly the impact of cardiovascular medications on survival.

Pulmonary Function Testing

Pulmonary Function Testing Methods and Techniques

Spirometry is the accepted standard for diagnosing airway obstruction, particularly in making the diagnosis of COPD. It is also useful in differentiating reversible and non-reversible airway obstruction when combined with a bronchodilator trial. Some studies have suggested that spirometry done in primary care settings can be useful, but the quality of the spirometry may be lacking, and this can affect interpretation.

Borg et al[59] measured how frequently spirometry in a primary care setting met the American Thoracic Society (ATS) criteria, and compared spirometry done by local users to that done by a trained specialist. Even after 14 hours of spirometry training, the primary care users failed to perform spirometry at a consistent level of acceptability. Acceptability criteria were often not met, but repeatability criteria were. The spirometers used did not display flow-volume and volume-time tracings in real time, and may have contributed to the poor rate of acceptability. Only 57% of maneuvers met all ATS/European Respiratory Society (ERS) criteria; 81% met the criteria for 2 acceptable efforts.

Masa et al[60] investigated whether spirometry could be performed remotely, utilizing personnel from a hospital to prompt the patient to perform the required maneuvers. Patients were randomized to be tested either in-person or remotely. Using 2 different approaches, intention to treat and protocol, there was almost no difference (bias) between the methods. The intention-to-treat grouping, analyzed using difference plots (Bland-Altman) showed the limits of agreement of about 350 mL for FVC and 300 mL for FEV_1. The protocol group yielded similar results. Online spirometry compared favorably; it took slightly longer (by about a minute) and required approximately one additional maneuver.

Body plethysmography to measure lung volumes is regarded as the accepted standard because it is minimally affected by maldistribution of ventilation, as compared to the gas dilution techniques. However, plethysmography can overestimate lung volume when the patient pants too rapidly or alveolar pressure is measured incorrectly for other reasons. Accurate lung volumes are used to assess air trapping and hyperinflation in patients who have obstructive lung disease, and have been recently used to evaluate response to therapies aimed at reducing these defects.

O'Donnell et al[61] compared computed tomography (CT) to lung volume measured via plethysmography and via helium dilution. They looked at a range of patients in 3 centers, including subjects with severe airway obstruction ($FEV_1 < 30\%$ predicted). The CT measurements were single maneuvers and measured total lung capacity directly, with the patient in a supine position. One center corrected for spirometric differences during the CT measurement. Helium dilution used a standard technique but was measured only once. Not surprisingly, CT derived lung volumes compared favorably with the helium dilution technique, and both were significantly lower than plethysmographically derived lung volumes. The mean difference in patients who had airway obstruction was approximately 1 L (plethysmography vs either CT or helium dilution). These data suggest that plethysmography may overestimate lung volumes even when done correctly, and that when lung volumes are used to make therapeutic decisions, the method of measurement may become important.

Predicted Values

Interpretation of spirometry depends on the use of appropriate reference data from a normal healthy population. The NHANES III reference set has been recommended for use in the United States, but has a lower age range of 8 years of age. In addition, separate regression coefficients are required to accommodate pediatric/adolescent subjects and adults. The variability of the common spirometric measures is assumed to be constant across ages in adults.

Stanojevic et al[62] used the lambda, mu, sigma (LMS) statistical modeling approach (as used to produce growth charts for children) to account for the variability in spirometric measures at each age and height. Data from other studies of young children were combined with the NHANES III data to extend the lower age limit to 3 years and provide a smooth transition between the youngest children, adolescents, and adults. This is particularly important because of the rapid increase in lung function during the first 10 years of life and the changes that occur during adolescence. These all-age equations account for the between individual variability (age-dependent). The largest variability is in children < age 11 years, but there is also increasing variability with advancing age (> 30 years). This approach uses z-scores, which take into account age and height related variability.

Lung function might be expected to change as a result of nutrition, environment, and availability of healthcare or other factors. As a result, predicted values might vary over time. ATS/ERS guidelines suggest that pulmonary func-

tion laboratories evaluate reference equations for local use, but it is not clear how large a sample population might be needed to perform this type of validation.

Quanjer et al[63] evaluated a large database collected as part of the Global Lungs initiative. Thirty spirometry data sets from whites over a period of 30 years were compared using GAMLSS (Generalized Additive Models for Location Scale and Shape) modeling to calculate mean z-scores for FEV_1. There does not seem to be a trend of either increasing or decreasing FEV_1 from the period 1980 to 2010. This finding was somewhat unexpected, but suggests that older reference equations remain valid.

Quanjer[63] also subdivided healthy subjects from a large population study (Health Survey for England) into different, randomly selected, smaller subsets to evaluate differences due to sample population and technique. When the data sets were large (> 1,000 persons), the z-scores for variables like FEV_1 were small. Small sample sizes resulted in increased z-scores. The authors concluded that at least 150 males and 150 females would be needed to validate reference values to avoid spurious differences due to sampling error. Unfortunately, this type of study is beyond the scope of most pulmonary function laboratories.

Although NHANES III has been recommended for use in the United States (for whites, African-Americans, and Hispanics) it has not been formally validated. A correction factor for Asian-Americans of 0.94 was based on 2 studies that included young and old subjects but not many in between. NHANES III was also not validated in patients older than age 80. Hankinson et al[64] used spirometry performed as part of the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study to address some of these issues. The equations for whites, African-Americans, and Mexican-Americans performed acceptably; the average values were slightly smaller than the predicteds but the differences were less than the repeatability criteria of 150 mL. The authors attributed these small differences to methodological differences. There was also excellent agreement for classifying abnormal lung function by the lower limit of normal (LLN). The largest discrepancies (observed-predicted) were seen in African-American men and in Hispanics of non-Mexican origin. Observed values for Asian-Americans were significantly lower than predicted values, even when the suggested 0.94 correction factor was applied. The authors suggest that a factor of 0.88 may be more appropriate for Asian-Americans, particularly those of Chinese ancestry. The differences for Asian-Americans tend to be less at age 70 and above. For subjects over age 80, the NHANES III predicteds underestimated the observed value (most likely survivor bias), but there were no extreme differences, so that NHANES III can be used without significant misclassification.

Natural History and Pulmonary Function in Health and Disease

FEV_1 percent of predicted is widely used to classify or categorize the severity of obstructive lung disease. FEV_1 is a predictor of all cause mortality as well as for mortality related to respiratory disease. The usual approach has been to arbitrarily select percent of predicted thresholds to classify severity (eg, 80% as normal, 50% separating moderate from severe).

Miller and Pedersen[65] evaluated spirometry data from 3 large studies: the University Hospital Birmingham (11,972, 53% male), the Copenhagen City Heart Study 1976–2002 (13,900, 46% male), and 1,095 COPD patients for whom survival data were available. The investigators compared various indices (percent of predicted, SR, FEV_1/Ht^3, FEV_1/Ht^2, and a new parameter, FEV_1Q) to see which best-predicted mortality. The new metric, FEV_1Q, expresses impairment as the number of turnovers of the nominal lower limit (based on the lowest 1 percentile) of lung function remaining. Instead of looking at how much function is lost, FEV_1Q looks at how much is left. The FEV_1Q and FEV_1/Ht^3 performed better than percent of predicted or even the SR. The percent of predicted fails because it is markedly different in young and old subjects with severe lung disease. The SR (z-score) has similar limitations. The authors recommend rethinking how to best categorize obstructive lung disease.

The FEV_1/FVC in children has been considered to fall with age, just as in adults, and this assumes that the ratio of residual volume to total lung capacity (RV/TLC) remains constant. Because of changes in the airways, body proportions, thoracic shape, and respiratory muscle function that occur during growth, the age dependence of FEV_1/FVC and RV/TLC is unknown. Quanjer et al[66] combined several large groups of children from around the world and fitted spirometry data for age, height, and sitting height (from 3 centers). In childhood, FVC outgrows TLC and FEV_1, leading to a fall in FEV_1/FVC and RV/TLC. However, these trends tend to reverse in adolescence. Sitting height reduces the differences in pulmonary function within and between various ethnic groups. The highest FEV_1/FVC ratios occur in the children who are shortest for their age. These changes need to be considered for interpretation of pulmonary function tests, particularly in adolescents where the FEV_1/FVC may plateau or even increase. Reference equations for children and adolescents need to account for sex, height, age, ethnicity, and ideally sitting height.

Interpretation of spirometry using the 95th percentile as the LLN may not detect mild air flow limitation. Reporting lung function decline to smokers has been suggested as a mechanism to encourage smoking cessation. The current literature is mixed, with most reports showing minimal

improvement in smoking cessation rates when lung age or spirometry results are used.

Hansen et al[67] assessed the population of smokers and non-smokers who participated in the NHANES III survey ($n > 9{,}000$). The odds that a given difference between observed and predicted came from a smoker versus non-smoker were calculated for FEV_1/FVC and FEV_1/FEV_6. The authors found evidence that air flow obstruction is observable at age 25 and markedly different by age 50 years. As FEV_1/FVC decreases by a few percentage points from the predicted, the odds increase to above 1. Calculating these odds that lung function has decreased suggests that subtle changes precede the fall into the lowest 5th percentile. Whether this is any more useful for convincing smokers to quit has yet to be proven. Another study[68] demonstrated that appropriate reference equations have to be used to predict lung age. Unfortunately, because of the wide variability of the FEV_1 and FEV_1/FVC ratio in healthy subjects, it is difficult to attribute increased lung age (lower observed than predicted) to smoking. It is also not appropriate to allow smokers whose FEV_1 is above their mean expected value to continue to smoke. Only serial measurements and trend analysis can tell whether an individual has an increased rate of loss of lung function.

COPD Controversy

The ATS/ERS interpretation guidelines recommend using a statistically valid LLN for the FEV_1/FVC, along with LLN for TLC and the diffusing capacity of the lung for carbon monoxide (D_{LCO}). Many clinicians still use the 0.70 fixed ratio for defining airway obstruction and 80% as the LLN for all other parameters (FVC, TLC, D_{LCO}). While the problems caused by using a fixed FEV_1/FVC ratio have been well documented over the past 5 years, the use of a fixed cut-off of 80% has persisted.

Miller et al[69] combined a large population of patients from 3 different countries and used 2 versions of the ATS/ERS algorithm to classify their disease patterns. The use of the fixed FEV_1/FVC ratio and 80% of predicted for FVC, TLC, and D_{LCO} was compared to using the LLN (5th percentile) of the same measures. Out of 11,413 patients, about 1,000 more patients were classified as abnormal by the percent-predicted method (3,904 vs 2,808). A total of 2,685 patients had discordant interpretations (23.5% of the entire group). Age and gender bias were noteworthy in the number of asthmatics and emphysema patients when fixed cut-off values were used. Although the ATS/ERS algorithm is somewhat arbitrary and simplistic, in this study it points out the significant differences that can occur depending on how normal is defined.

The LMS statistical method is a new approach that defines the LLN for FEV_1/FVC as the 5th percentile of the distribution of z-scores. The clinical validity of this threshold for defining COPD is unknown. The LMS method takes into account the between-individual variability and more accurately describes how spirometric variables change with age. Using LMS, the z-score accounts for the median (mu) representing how the spirometric variable changes with the predictor variable; for the coefficient of variation (sigma), which models the spread of spirometric reference values and adjusts for non-uniform dispersion; and for skewness (lambda), which models how the variables differ from a normal distribution using a box-Cox transformation.

The LMS-LLN5 is a carefully defined statistical definition of normal, and Vaz Fragoso et al[70] looked to see if it correlated with death and respiratory symptoms in a subset of NHANES III participants (40–80 years, whites with mortality data through 12/31/2000). Subjects were stratified by their FEV_1/FVC set at progressively higher percentiles. Adjusted hazard ratios for death and odds ratios for respiratory symptoms only exceeded 1.0 for those with ratios $<$ LMS-LLN5 (subjects in the LMS-LLN25 percentile were used as the reference group). Both GOLD and the standard LLN (5th percentile) tend to overestimate the presence of air flow obstruction, particularly in the oldest age groups. The standard LLN does not account for the increasing variability seen in healthy older subjects. In other words, the LMS-LLN5 tends to be even lower than the 5th percentile as normally calculated. The authors conclude that in whites ages 40–80 years, an $FEV_1/FVC <$ LMS-LLN5 identifies persons with increased risk of death and prevalence of respiratory symptoms. The LMS-LLN5 should be used as the threshold for establishing COPD.

There has been a great deal of evidence recently published showing that FEV_1/FVC is age dependent, and is also influenced by height, gender, and ethnicity. Use of the fixed cut-off of 0.70 to define airways obstruction misclassifies older subjects as having COPD (false positives) and younger subjects as being normal when they may have asthma or early COPD (false negatives).

Quanjer et al[71] sent an open letter to the members of the GOLD scientific committee requesting that they change the definition of mild airway obstruction. To quote from the letter, "We are therefore appealing to you, members of the GOLD committee, to change the method by which mild airway obstruction is defined by the GOLD guidelines in order to abandon the fixed ratio forever in favor of the lower limit of normal." It references 40 studies or editorials that call the fixed ratio into question. There is a long list of supporting organizations and 147 signatories from 23 countries, including physicians, respiratory scientists, and respiratory therapists involved in lung function testing. Although a very good case can be made for using a statistically valid LLN, the argument can be made that COPD is never diagnosed in an individual patient without

consideration of the history and physical presentation in addition to spirometry. But the GOLD guidelines have become so entrenched that epidemiologic studies and multicenter drug trials have used them for inclusion/exclusion criteria, introducing significant bias into otherwise well conceived scientific investigations.

Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is a common and serious complication in the intensive care unit. VAP is typically associated with greater costs and increased mortality. Given these facts, the prevention, diagnosis, treatment and monitoring of VAP have been a frequent topic in the recent literature.

The Tube, the Intubation Route, and the Cuff

While VAP derives its *nom de guerre* from association with the ventilator, the ventilator is probably only a bystander. Translaryngeal placement of an endotracheal tube appears to be the real risk factor, representing a direct conduit for contamination of the lower airway. Modifications of the structure and material composition of the tube and cuff have occurred in the last year in an effort to prevent VAP.

The original North American Silver Coated Endotracheal Tube Study (NASCENT), published in 2008, demonstrated a reduction in VAP rate in patients intubated with a silver-coated tube.[72] More recently, Rello et al[73] evaluated silver and non-silver-coated tubes in a series of pre-clinical models of early VAP. They demonstrated reduced biofilm adherence to the silver-coated tubes, continued presence of the silver coating out to 21 days, and reduced colonization of silver tubes compared to uncoated tubes. These studies included animal, in vitro, and patient data. Together these data suggest that the silver-coated tube has characteristics that disrupt the early pathogenesis of VAP. In a secondary analysis of the NASCENT trial, Afessa et al[74] found that the presence of the silver coated tube was associated with an improved mortality. Patients using traditional tubes had a greater incidence of sepsis, perhaps leading to the mortality difference. These findings suggest that the silver tube, used with appropriate antibiotic coverage, reduces multiple-drug-resistance and accumulation of biofilm, and improves outcome. This is a novel finding, as previous studies without silver-coated tubes demonstrated an increased mortality with late onset of VAP.[75] These findings have been debated and require further validation.[76-78]

Lacherade et al[79] undertook a large multicenter trial of continuous subglottic suction endotracheal tubes versus conventional endotracheal tubes. They found that use of the subglottic suction tube was associated with a reduced incidence of both early and late onset VAP, with an absolute risk reduction of 10.8%. They also noted that the use of subglottic suctioning was not associated with evidence of tracheal wall injury or a difference in re-intubation rate secondary to airway edema. The latter finding is important, as this had been an area of concern related to the use of these tubes.

Conventional wisdom has favored tracheostomy over long-term endotracheal intubation for reduction of VAP. However, conflicting data have been presented, which may represent differences in the patient populations studied. Terragni et al[80] performed a randomized controlled trial of early versus late tracheostomy in 419 patients and found no difference in the incidence of VAP. Nearly every early tracheostomy study suffered from design problems and practical limitations. The important question may not be when (early or late), but who (head injury, the elderly, etc).[81]

The introduction of high-volume low-pressure endotracheal tube cuffs 30 years ago was welcomed as a solution to tracheal injury from high-pressure, low-volume cuffs. More recently, cuff designs have changed to eliminate the common invagination of high-volume low-pressure cuffs, which create a conduit for aspiration of subglottic secretions. Pitts et al[82] reported reduced leakage around new cuff designs in a silicone model of the trachea. While these in vitro findings support previous findings, limitations of the model prevent generalization of the findings to patients.[83,84] For example, Dave et al[85] found that lubricating cuffs in these in vitro models significantly improves the seal. Whether these findings can be repeated in vivo remains to be determined.

Mechanical Ventilation

Noninvasive ventilation (NIV) probably derives a number of its advantages from elimination of the artificial airway. A Cochrane review by Burns et al[86] found that NIV is associated with a reduction in VAP, mortality, and ICU days, compared to invasive ventilation. In this analysis the relative risk for developing VAP was 0.29 (95% CI 0.19–0.45) in favor of NIV. These findings should be tempered by the preponderance of patients with chronic lung disease in this analysis. Extrapolation to other disease states should be made with caution.

A multicenter, retrospective review of 400 German ICUs, including over 78,000 patients, found that NIV was associated with a VAP rate of 1.6 cases per 1,000 ventilator days. The VAP rate in invasive ventilation was 5.4 cases per 1,000 ventilator days.[87] While these findings support the Cochrane review, the number of patients receiving NIV in these centers was remarkably low. This probably represents a slow adoption of NIV, even in those patients most likely to benefit.

In both in vivo and in vitro studies, the use of PEEP is associated with reduced aspiration around the endotracheal tube cuff.[83,85,88] It is likely that new cuff designs and the use of a minimum level of PEEP combine to reduce silent aspiration. A recent trial of airway pressure release ventilation suggests a reduced VAP rate through a similar mechanism.[88] This finding provides additional evidence for the use of PEEP in mechanically ventilated patients.

The Bundle

The use of VAP bundles, a collection of clinical standards, has been promoted as an effective method for reducing VAP. Rello et al[89] developed a recent bundle with input from a multidisciplinary group using multicriteria decision analysis, which is a technique that supports decision making when numerous and conflicting evaluations are assessed, by weighting and prioritizing procedures. They evaluated procedures in 2 groups: the diagnosis of VAP, and the treatment of VAP. In the diagnostic section the bundle consisted of (in order of importance): early chest radiograph, immediate Gram-stain results, quantitative microbiology prior to antibiotic treatment, blood cultures, invasive specimen sampling prior to antibiotic treatment, and determination of intracellular organism in alveolar lavage fluid. The VAP treatment bundle consisted of (in order of importance): immediate antibiotic treatment following sampling, empirical antibiotic therapy based on local pathogens, de-escalation of antibiotic therapy following identification of organisms, assessment of response to therapy within 72 hours, and use of monotherapy in patients with low risk for multiple-drug-resistant organisms. Additional studies support the use of bundles and, importantly, monitoring of adherence and use of quality improvement to maximize adherence.[90,91]

Cost

The financial burden of VAP is a concern for patients, caregivers, health systems, and payers. While a case of VAP is often said to add $40,000 to hospital costs, a paper by Magret et al[92] found no difference in ICU stays or costs associated with VAP in trauma patients. In fact, the trend was for lower mortality in trauma patients with VAP. Clearly, patient population affects the response to VAP. Restrepo et al[93] found contradictory findings, suggesting VAP increased costs by around $20,000 per case. Interestingly, respiratory therapy charges were not different between groups. A main concern of hospitals is the recent suggestion that VAP should be a never event. Data from the NASCENT trial suggest that, while a VAP rate of zero is a laudable goal, it is probably unobtainable.[91]

Miscellaneous

Use of adjunctive aerosolized antibiotics for the treatment of VAP continues to be explored. Reducing the systemic complications of aminoglycosides is a commonly mentioned advantage. Czosnowski et al[94] retrospectively reviewed their adjunctive aerosol therapy use in a trauma ICU and found microbiologic success in 77% of patients. Aerosolized antibiotics were used predominantly in patients failing intravenous monotherapy. Prone positioning, lateral rotation, and lateral position with horizontal position of the endotracheal tube have been described with varying degrees of success in reducing VAP.[95-97]

The use of probiotics to alter gastrointestinal flora and alter VAP rates has been reported, but this idea is early in development.[98-100] Finally, there continues to be support for a reduced frequency of ventilator circuit changes.[101,102]

Summary

In this paper the important recent literature on asthma, COPD, pulmonary function testing, and VAP is reviewed. It is our hope that this will help to familiarize the reader with the important literature in these subject areas.

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