A New ATS Committee

Competing in the Marketplace of Ideas

During the past 10 years, the American Thoracic Society (ATS) has directed considerable efforts toward optimizing the creation and dissemination of official ATS documents and enhancing the implementation of the clinical and scientific recommendations these documents propose. These efforts have culminated in the ATS Board of Directors' approval of a new committee, the Documents Development and Implementation Committee, and a new editor position, the ATS Documents Editor. The first author (H.J.S.) of this editorial is honored to have been proposed by the search committee and approved by the ATS Board as the inaugural Documents Editor.

The Documents Editor serves a collaborative role in coordinating the efforts of the ATS Board of Directors, elected officers, journal editors, assemblies, relevant committees, and staff to manage the development, review, publication, dissemination, and implementation of official ATS documents. Previously, the Documents Coordinator, Dr. Gerard Turino, who will continue to support the document process, ably performed these duties. The increasing complexity of developing and implementing ATS documents, however, has underscored the need to consolidate efforts within this new position and a new committee.

THE ROLE OF THE DOCUMENTS EDITOR

The duties of the Documents Editor include several specific assignments. The first task will be to work with the ATS President and President-Elect to appoint members to the new ATS Documents Development and Implementation Committee, for which the Documents Editor will serve as chair and Dr. Gerald Turino as vice-chair. This committee will support the Documents Editor and the Board of Directors to optimize the outcomes of the following Document Editor's responsibilities:

- Monitor and coordinate the development of official ATS documents, such as conference proceedings and statements, from inception to completion.
- Assist assemblies in identifying topics in need of official documents.
- Serve as a methodology resource for document developers to provide guidance for evidence identification, evaluation of the quality of evidence, and formatting specific recommendations according to evidence-based methods and clear linking evidence to recommendations.
- Advise the Board of Directors and the ATS journal and web editors regarding format of publication.
- Formulate strategies of dissemination and implementation of official documents.
- Work closely with the ATS committees to promote document implementation.
- Monitor the quality and impact of ATS documents.
- Work with sister organizations in developing joint documents.
- Suggest a uniform system for grading the quality of evidence and strength of recommendations.

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LEGACY OF EXISTING AND NEW DOCUMENTS

These new efforts build on a long legacy of ATS documents that have contributed greatly to the advancement of respiratory medicine by standardizing techniques (e.g., statements on pulmonary function testing), defining disease (e.g., statements on acute respiratory disease and idiopathic fibrosis), promoting public health (e.g., workshops on lung disease and the environment), and guiding clinical practice (e.g., clinical practice guidelines on community-acquired pneumonia and treatment of tuberculosis) (1, 2). The marketplace of ideas, however, constantly evolves and has become more demanding; future official documents must adhere to higher methodology standards and more innovative implementation techniques for the ATS to continue its rich tradition of advancing science and health. The Documents Editor will serve ATS members by complementing their *content* expertise with document *development and implementation* expertise to limit inconsistencies in the methodologic quality and, therefore, promote the effectiveness of our ATS documents. These efforts can only be successful if they assist but do not constrain the talents of our ATS membership at large. The Documents Committee will continue—as a core strength of the ATS documents development process—our "bottom up" approach that capitalizes on the creativity, expertise, and commitment of our members to identify and develop topics for official documents.

WHAT THE NEW DOCUMENTS EDITOR AND COMMITTEE SEEK TO ACHIEVE FIRST

Although the ATS has provided for nearly a decade methodology resources for guiding the development of official documents (3, 4), considerable gaps exist in the application of these resources to actual document development. In the instance of clinical practice guidelines, for example, some guidelines contain insufficient descriptions of how document authors obtained evidence that formed the basis of their recommendations and lack transparency between recommendations and the supporting evidence. These shortcomings would not always withstand tests of truly evidence-based clinical practice guidelines, which require explicit definitions of the question that the guideline addresses, eligibility criteria for the evidence to be considered, graded recommendations for action, and several other essential elements (5, 6). To achieve adherence to ATS standards for evidence-based documents, the Documents Editor will work with the Board of Directors to refine the methodology for ATS guideline development. The Documents Editor will be guided by the Documents Committee and will report through the ATS Executive Committee to the Board of Directors.

THE DOCUMENTS DEVELOPMENT AND IMPLEMENTATION COMMITTEE

This committee, comprised of 15 to 20 ATS members with expertise and interests related to document development, will recommend to the Board of Directors policies regarding the development of official ATS documents, serve as liaison with other organizations for joint documents, prepare guiding materials for document developers, manage conflict-of-interest concerns,

design implementation strategies for documents, and identify strategies for measuring the impact of documents after their publication.

Building on the example of clinical practice guidelines, the committee will devote considerable effort to identifying and establishing a grading system to evaluate the quality of evidence and the strength of recommendations for ATS clinical practice guidelines. Various efforts of diverse organizations and societies to develop grading systems have been underway, but a systematic application of one grading system that allows users to retain understanding while switching from one guideline to another—in particular, on an international level—is long overdue (7). The Documents Editor will work with the Grading of Recommendations Assessment, Evaluation, and Development (GRADE) Working Group, which is an international effort to standardize the grading of evidence and recommendations (8).

The Documents Development and Implementation Committee will also assist the ATS in identifying current scientific and health care issues for which documents should be considered. On the horizon will be efforts to develop a standard development and reporting methodology for scientific documents that would derive from work already conducted for randomized trials (i.e., Consolidated Standards of Reporting Trials [CONSORT]) (9), diagnostic testing (i.e., Standards for Reporting of Diagnostic Accuracy [STARD]) (10), and systematic reviews (i.e., Quality of Reporting of Meta-Analyses [QUORUM]) (11).

FOCUS ON IMPLEMENTATION

Implementation of what documents intend to achieve will be a key interest of the Documents Editor and Committee. The Institute of Medicine's challenge for us to cross the quality chasm represents a call for action to the ATS and healthcare systems in general (12). Effective implementation of evidence-based recommendations represents one bridge across this chasm and depends on clinicians being aware of the recommendations, accepting them, agreeing with them, finding them applicable, and applying them correctly if the resources for the recommendations are available (e.g., a new technology) (13). The science of evidence dissemination and implementation is rapidly evolving (14).

We anticipate that the Documents Committee can catalyze increased interest among ATS membership in these new fields of implementing evidence-based practice and translational science. We also plan to promote access to funding from public agencies (e.g., Agency for Healthcare Research and Quality) for support of our larger guideline development projects. These efforts can guide the expertise of ATS members toward becoming more involved in national efforts to implement best clinical practices, improve processes of care, and develop measures of the quality of care delivered. These latter interests become increasingly more important to ATS members as Medicare and third-party payers adopt value-based reimbursement ("pay-for-performance") systems, which depend on measures of quality performance. In addition, specialty boards will incorporate professional society statements to develop their materials and metrics for maintenance of certification.

Yet the committee will remind the ATS that *people* take care of patients and advance science and every patient and circumstance is unique. Evidence alone does not make complex decisions, and unconsidered application of clinical practice guidelines and other recommendations can do more harm than good or prove to be infeasible (15, 16). We look forward to this new ATS endeavor and will welcome feedback from ATS members, our sister societies, and our journal readership regarding the future direction of our official documents.

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Low Testosterone in Chronic Obstructive Pulmonary Disease

Does It Really Matter?

Middle-aged and elderly men exhibit a decline in the concentration of serum testosterone (1). When excessive, this decline may contribute to diminished energy level, libido, bone density, and muscle mass (2). This constellation of signs and symptoms has been termed late-onset hypogonadism, symptomatic late-onset hypogonadism, androgen deficiency in the aging male, or andropause (3). The observation that many patients with COPD, most of whom are middle-aged or elderly, fit the profile of late-onset hypogonadism (4–6) has spurred a flurry of research on the incidence (6–8), functional impact (6, 8–10), and possible treatment (11) of this abnormality.

In this issue of the *Journal* (pp. 1105–1111), Van Vliet and coworkers (8) extend our knowledge on late-onset hypogonadism in men with COPD. They compared, for the first time, patients with COPD and age-matched control subjects. Half of the 78 patients with COPD had low levels of free testosterone, whereas a quarter of the 21 control subjects were hypogonadal. Does this mean that late-onset hypogonadism has a high prevalence in patients with COPD? Probably not. First, the prevalence of hypogonadism in the small control group of Van Vliet and colleagues is much lower than the 34 to 40% prevalence of hypogonadism for subjects in their 60s (1, 12) and than the near 70% prevalence for subjects in their 70s (1) reported in population studies in North America (1) and Europe (12). Second, when the data of Van Vliet and colleagues are pooled with three other recent studies (6, 7, 10), the overall prevalence of hypogonadism in men with COPD is 43%. This is within the range reported in population studies of generally healthy men of the same ages (1, 12). Third, the conclusion that late-onset hypogonadism in men with COPD is not something unique to these patients—and probably not different from late-onset hypogonadism in the general population—is further supported by the lack of correlation between testosterone levels and severity of obstruction (6, 8) or with potential causes of hypogonadism specific to patients with COPD, such as hypoxemia or glucocorticoid therapy (6, 8, 10). The similar prevalence of comorbidities in the hypogonadal and eugonadal men with COPD, reported for the first time by Van Vliet and colleagues, further supports the possibility that hypogonadism in these patients is not a different entity from late-onset hypogonadism in the general population.

In their investigation, Van Vliet and coworkers (8) noted a correlation between quadriceps strength and testosterone concentrations. This finding adds information to a complex and often contradictory body of literature (9–11, 13, 14). For instance, Debigare and associates (10) reported that the prevalence of hypogonadism among men with COPD is equivalent among patients with and without muscle wasting. Similarly, we (9) recorded no difference in quadriceps strength (and endurance) between hypogonadal and eugonadal men with COPD. In addition, when Bhasin and colleagues (13) administered a long-acting gonadotropin-releasing hormone agonist to induce hypogonadism in elderly men and then supplemented the men with subtherapeutic doses of testosterone enanthate, they found no difference in fat free mass or muscle strength. When the same investigators doubled the circulatory levels of total and free testosterone by administering higher doses of testosterone enanthate, the increases in fat free mass and strength were within the noise of the measurement. The same team of investigators, however, reported a 17% increase in quadriceps strength (and endurance) when administering 100 mg/week of testosterone enanthate for 10 weeks to men with COPD undergoing resistance training (11). It is not known why low testosterone should cause decreased strength in some series and not in others, nor whether the statistical differences in quadriceps strength—when present—are clinically important.

Despite less quadriceps strength among their hypogonadal patients, Van Vliet and colleagues (8) reported equivalent exercise capacity (6-minute walk distance) in the two groups of patients. This result confirms previous observations of equivalent exercise capacity, quantified either as 6-minute walking distance (6) or maximal bicycle ergometry (9), in men with COPD with and without hypogonadism. The similar exercise performance in the two groups is also consistent with the observation that administration of anabolic steroids to unselected patients with COPD (15, 16) or testosterone enanthate to men with COPD and variable testosterone levels (11) produces no improvement in whole body exercise capacity.

A crucial question is whether the results of Van Vliet and coworkers (8) support the use of testosterone supplementation in men with COPD who have low testosterone levels. The investigators express caution. Men who have COPD and low testosterone levels do not differ from their eugonadal counterparts in respiratory symptoms, quality of life, respiratory muscle strength and endurance, and exercise capacity (6, 8, 9). Therefore, it is difficult to justify that goals of replacement therapy are to improve these parameters. Replacement therapy does not increase exercise capacity or respiratory muscle strength in these patients (11). The use of testosterone replacement therapy to increase quadriceps strength in patients participating in rehabilitation programs is promising (11), but requires larger trials.

The caution expressed by Van Vliet and colleagues (8) on whether (or not) to advocate testosterone replacement in men with COPD and low testosterone levels reflects the ongoing controversy regarding indications for testosterone replacement in older men in general (2, 3). Long-term testosterone supplementation can be associated with side effects, including increase in hematocrit, sleep apnea, and prostatic hypertrophy (2, 3). The effects of testosterone administration on the risk of atherosclerotic heart disease and prostate cancer remain unknown (2, 3) because all current studies are underpowered to answer these questions. For example, more than 6,000 elderly hypogonadal men randomly assigned to receive testosterone or placebo for 6 years would be necessary to determine whether testosterone treatment increases the risk of prostate cancer by 30% (2). In a recently published report from the Institute of Medicine, an expert committee concluded that unless more convincing studies are published, there is currently insufficient evidence to support testosterone therapy in older men (the case of most patients with COPD) (2).

So, does it matter if a man with COPD has low testosterone levels? The question raises the issue of whether clinically important functional differences between hypogonadal and eugonadal patients do exist, which, in turn, could have important therapeutic implications. For some clinical aspects, the accumulating evidence suggests that men with COPD and late-onset hypogonadism are not different from their nonhypogonadal counterparts. There-

fore, if testosterone is administered, it would be unclear what therapeutic effects should be monitored. Despite these considerations, several questions remain unanswered. For example, would men with COPD and low testosterone levels benefit from long-term testosterone therapy to treat osteoporosis? Does low testosterone level affect sexual function, intellectual capacity, or mood in men with COPD? Should testosterone be used during rehabilitation?

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Smoking
An Injury with Many Lung Manifestations

Idiopathic interstitial pneumonias are a group of interstitial lung diseases that lead to progressive scarring of the alveolar interstitium, respiratory insufficiency, and, in many cases, death. In 2002, the American Thoracic Society and European Respiratory Society published a joint statement with the goals of standardizing classification as well as providing definitions and criteria for the diagnosis of the idiopathic interstitial pneumonias (1). This statement defined a group of seven clinical, radiographic, and histopathologic patterns of unknown etiology, which were "sufficiently different from one another to be designated as separate disease entities" (1). Idiopathic pulmonary fibrosis, the most common of the idiopathic interstitial pneumonias, is defined as a chronic fibrosing interstitial process of unknown cause limited to the lungs and associated with a surgical lung biopsy showing a histologic pattern of usual interstitial pneumonia. Many non-idiopathic clinical conditions can be associated with a histologic pattern of usual interstitial pneumonia, such collagen vascular disease, drug toxicity, asbestos exposure, chronic hypersensitivity pneumonitis, and familial idiopathic pulmonary fibrosis. Although these clinical conditions are technically not idiopathic interstitial pneumonias, they can provide useful insights into the pathobiology of these disorders.

In this issue of the *Journal* (pp. 1146–1152), Steele and coworkers present data from a large cohort of subjects with familial interstitial pneumonia as defined by the presence of two or more cases of probable or definite idiopathic interstitial pneumonia in related individuals within three decades (2). They identified 111 families and were able to obtain data from 708 of 945 (75%) subjects. Subjects were asked to complete a questionnaire, obtain a chest radiograph, and undergo measurement of carbon monoxide diffusing capacity. A high-resolution computed tomography scan was requested in subjects with self-reported interstitial pneumonia, significant dyspnea, or abnormal pulmonary function/chest radiograph. A surgical lung biopsy was recommended in individuals with a high-resolution computed tomography scan suggestive of idiopathic interstitial pneumonia. Older age, male sex, and a history of ever smoking were identified as significant risk factors for the development of interstitial pneumonia.

Although the cause of pulmonary fibrosis is unknown, it is plausible to speculate that the pathogenesis involves both an injury to the pulmonary epithelium and an abnormal host response to healing (3). Previous case-control studies have identified smoking as a risk factor for the development of idiopathic pulmonary fibrosis, particularly in association with environmental exposures (4–6). The clinical series from Steel and colleagues adds additional evidence that smoking is associated with the development of interstitial pneumonia, even though correlation between sibling pairs was lacking.

Given the complexities of fibrotic pathways, we can speculate that defects in any number of regulatory systems can result in a predisposition to fibrosis. Cigarette smoke may prime the lung toward a fibrotic response when other injuries are encountered (7). The lack of correlation within sibling pairs in this study could be explained by the presence of multiple recessive mutations with incongruent distribution among siblings or perhaps a differential response to "second" injuries, environmental or infectious. Indeed, only a minority of families in this study appeared to demonstrate an autosomal dominant pattern of inheritance. A very important point of this study, which has also been suggested by other clinical series, is that cigarette smoking participates in the etiology of a spectrum of lung diseases, including fibrotic lung disease. This association between cigarette smoking and fibrotic lung disease appears to be true for both the sporadic and inherited forms of the disease.

Using clinical, radiographic, and pathologic tools, it is possible to separate the idiopathic interstitial pneumonias into separate "diseases" with varied phenotypes and prognoses (1). A surprising feature in this study, at least at face value, is that 45% of families had more than one type of interstitial pneumonia. The presence of multiple genes, interacting with each other, could explain why varying clinical phenotypes (1) can be seen within families where the genetics would be expected to be similar (2) and in families where only a single genetic mutation, such as surfactant protein C (8), was identified.

A weakness of this study is that only a minority (78/713, 11%) of patients had their diagnosis confirmed by surgical lung biopsy. Surprisingly, despite being younger than patients without a surgical lung biopsy, their mortality was higher! As a group, 67 patients had idiopathic pulmonary fibrosis at biopsy; 181 patients had idiopathic pulmonary fibrosis on the basis of clinical features and high-resolution computed tomography. Numerous studies have highlighted the diagnostic value of high-resolution computed tomography in the diagnosis of pulmonary fibrosis (9–12), so it is likely that the diagnostic classification of these patients was accurate. What is not known are the radiographic characteristics (i.e., presence of honeycombing) for the patients with a surgical lung biopsy. It is plausible to speculate that the patients undergoing surgical lung biopsy had atypical radiographic features for idiopathic pulmonary fibrosis and likely lacked honeycombing. What is puzzling is that patients with radiographically demonstrated honeycomb change are known to have increased mortality (10, 12, 13). Even if the patients with and without a surgical lung biopsy had similar radiographic features, we would at least expect a similar mortality. Perhaps genetic anticipation or the accumulation of multiple genetic mutations resulted in an earlier and more aggressive manifestation of disease in these patients.

A practical point for our day-to-day practice is the need for a heightened suspicion for idiopathic interstitial pneumonias in patients with a positive family history. Approximately 8% of subjects participating in this survey who reported their clinical status as "unaffected" had definite or probable interstitial pneumonia when they were evaluated. Although, there is currently no effective therapy for idiopathic pulmonary fibrosis, many therapeutic trials are underway (14) and others are in the design phase. Most investigators believe these interventions are more likely to work in patients with mild or moderate disease. Maintaining a high level of suspicion for interstitial pneumonia, especially in patients with a pertinent family history, should help identify patients with an early stage of disease who could be eligible for participation in research trials.

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