

## Clinical Practice Guidelines for Chronic Obstructive Pulmonary Disease: A Review and Comparison of Current Resources

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### Summary

**The first clinical practice guidelines (CPGs) for the assessment and management of patients with chronic obstructive pulmonary disease (COPD) were published 30 years ago. These and subsequent CPGs issued by professional societies and other groups prior to 2000 were consensus recommendations based on expert opinion and available studies, and they have been criticized for being inconsistent and not explicitly evidence-based. The Global Initiative for Chronic Obstructive Lung Disease (GOLD), a joint project of the National Heart, Lung, and Blood Institute and the World Health Organization, released the first of a new generation of rigorous, evidence-based COPD guidelines in 2001. Since that time several other CPGs, notably those developed jointly by the American Thoracic Society (ATS) and the European Respiratory Society (ERS), and by the British National Collaborating Center for Chronic Conditions and Institute for Clinical Excellence, have also become available. While previous COPD guidelines had different severity-grading systems and differed in their therapy recommendations, the new CPGs are remarkably consistent and have very**

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few areas of clinically relevant discrepancy. All are available free via the Internet, provide for regular revision and updating, and include materials for patients and the public, as well as for health-care providers. Although the GOLD and ATS-ERS guidelines both have international authorship and are intended for worldwide use, implementation of many of their recommendations (such as the requirement for spirometry in diagnosis and staging, an escalating management scheme that includes expensive inhaled medications and pulmonary rehabilitation, and consideration for lung-volume reduction surgery) remains beyond the reach of many patients and health care systems. *Key words:* chronic obstructive pulmonary disease, COPD, practice guidelines, spirometry, staging, smoking cessation, management, bronchodilators, corticosteroids, oxygen therapy, rehabilitation. [Respir Care 2006;51(3):277–288. © 2006 Daedalus Enterprises]

## Introduction

Practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.<sup>1</sup> Evidence-based medicine is an approach to clinical problem-solving that demands careful examination of the evidence, using formal rules applied in an explicit manner.<sup>2,3</sup> Evidence-based clinical practice guidelines (CPGs), a natural combination of these, with both evidence and instructional components,<sup>4</sup> represent the present ideal for bringing current scientific knowledge to the clinic and bedside. Recent decades have witnessed an explosion of publications about chronic obstructive pulmonary disease (COPD), which have both expanded our knowledge base and increased available management options. In this context the need for CPGs is clear, and a substantial number of them are now available. In this article I review the history of CPGs for managing patients with COPD, compare the recommendations of current guidelines in selected areas of management, and then comment on the extent to which available CPGs are evidence-based, accessible to potential users, and applicable in different contexts of practice. Although current guidelines also address management during acute illness, including mechanical ventilation and other aspects of critical care, the focus of this review is on the assessment and management of clinically stable patients.

## History of Guidelines for COPD

Current CPGs build on earlier guidelines and consensus statements whose foundations and previous versions go back several decades. The first attempts by professional groups to standardize concepts, definitions, and diagnostic criteria for what we now refer to as COPD took place in the late 1950s in Great Britain,<sup>5</sup> and shortly thereafter in the United States.<sup>6</sup> Early work on an overall approach to managing patients with COPD by Petty,<sup>7</sup> Miller,<sup>8</sup> and others in the United States was facilitated by an initiative of the Department of Health, Education, and Welfare (now

the Department of Health and Human Services) to determine the effectiveness of comprehensive management and establish standards for care.<sup>9</sup>

One of the earliest clinical guidelines to receive widespread dissemination was funded by the National Science Foundation and published in 1975.<sup>10</sup> This consensus report reflected the state of the art of its time, both in scientific understanding of COPD and in the clinical approach to patient care. Most of the drugs have changed in the intervening years, and a few of the included topics (such as the clinical use of tests of small-airways function) are no longer considered relevant, but nearly all of the concepts and modalities discussed in that publication remain in the current guidelines. It stressed the primary role of spirometry in confirming the presence of airflow obstruction in order to make the diagnosis of COPD. It emphasized a multidisciplinary approach to patient care that prominently involved respiratory therapists, nurses, and other nonphysicians. The multi-modality approach to overall management focused on activities of daily living and aspects of quality of life rather than primarily on physiologic improvement or attempts to alter the disease's natural history. Included were discussions of patient education, smoking cessation (albeit in only one brief paragraph), immunizations, nutritional support, and the importance of social and community factors in optimally managing people with COPD.

A more comprehensive document based on the National Science Foundation project was later published as a monograph by the American College of Chest Physicians.<sup>11</sup> However, although an increasing number of research papers on COPD and its management appeared (Fig. 1), very few new CPGs<sup>12</sup> were published until the 1990s. During that decade, however, numerous professional societies and other groups issued guidelines on the diagnosis and management of COPD.<sup>13–29</sup> Most influential among these, at least for clinicians in North America, were the 1995 American Thoracic Society (ATS) standards statement,<sup>15</sup> the consensus statement of the European Respiratory Society (ERS) of the same year,<sup>16</sup> and the 1997 guidelines of the British Thoracic Society (BTS).<sup>21</sup>

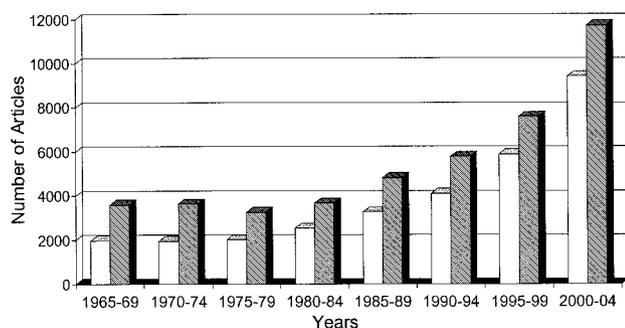


Fig. 1. Total number of articles listed in PubMed under the search terms "COPD OR emphysema OR chronic bronchitis" for each 5-year period between 1965 and 2005 (through November 21, 2005). The white bars represent articles in English, and the hatched bars represent all cited articles.

Table 1. Comparison of Spirometric Criteria for Disease Severity in 3 Prominent COPD Guidelines From the Mid-1990s, Using FEV<sub>1</sub> as a Percentage of the Predicted Value

| Severity | FEV <sub>1</sub> Percent of Predicted |       |       |
|----------|---------------------------------------|-------|-------|
|          | ATS                                   | BTS   | ERS   |
| Mild     | ≥ 50                                  | ≥ 60  | ≥ 70  |
| Moderate | 35–49                                 | 40–59 | 50–69 |
| Severe   | < 35                                  | < 40  | < 50  |

COPD = chronic obstructive pulmonary disease

FEV<sub>1</sub> = forced expiratory volume in the first second

ATS = American Thoracic Society COPD guideline<sup>15</sup>

BTS = British Thoracic Society COPD guideline<sup>21</sup>

ERS = European Thoracic Society COPD guideline<sup>16</sup>

Ferguson carried out an in-depth comparison of the ATS, ERS, and BTS guidelines in 2000.<sup>30</sup> He noted that while the ATS document was the most comprehensive and thoroughly referenced of the three (the others consisting more of overviews), all relied primarily on consensus opinion and empirical recommendations, and none was explicitly evidence-based. The target audience for the ERS guideline was respiratory specialists, whereas the ATS and BTS guidelines were intended for use by generalists and specialists in other disciplines. Overall, Ferguson found a high degree of agreement between the 3 CPGs with respect to both subjects covered and areas emphasized. However, as he pointed out, there were important differences in spirometric criteria for mild, moderate, and severe obstruction (Table 1). A patient with a forced expiratory volume in the first second (FEV<sub>1</sub>) of 45% of the predicted value would be classified as having severe disease by ERS criteria, but moderate disease by ATS and BTS criteria. Similarly, with an FEV<sub>1</sub> of 55% of predicted, the same patient would have moderate disease according to the BTS and the ERS but only mild disease according to the ATS.

Although the ATS,<sup>15</sup> BTS,<sup>21</sup> and ERS<sup>16</sup> guidelines agreed in general with respect to pharmacologic therapy for patients with clinically stable COPD, there were differences among them that implied differences in management. All recommended inhaled short-acting bronchodilators as primary therapy for airflow obstruction. However, the BTS<sup>21</sup> and ERS<sup>16</sup> documents provided no recommendation for the choice between  $\beta$  agonists and anticholinergics (while noting the greater potential for adverse effects with the former), whereas the ATS guideline<sup>15</sup> recommended  $\beta$  agonists for as-needed use and anticholinergics for scheduled administration. Long-acting inhaled bronchodilators were described by the ATS and ERS as potentially useful for nighttime awakening and early-morning symptoms, while the BTS cited a need for further studies before any recommendation could be made. The ATS was more supportive of theophylline as a second-line therapeutic agent than were either the BTS or the ERS. All 3 guidelines recommended long-term oral corticosteroid administration only for patients shown to respond favorably to these agents. With respect to inhaled corticosteroids, the BTS and ERS guidelines recommended them if patients were proven "responders," whereas the ATS made no recommendation, pending further study results.

A thoughtful analysis of COPD CPGs released during the 1990s was published by Lacasse and colleagues.<sup>31</sup> In their evaluation of 15 guidelines,<sup>13–25,28,29</sup> they found several areas of potentially important disagreement. These areas included the preferential use of  $\beta$  agonists versus anticholinergics for first-line bronchodilator therapy, the indications for mucolytic agents, the role of inhaled corticosteroids, the use of oxygen therapy for patients with transient desaturation during sleep or exercise, and recommendations for lung-volume-reduction surgery. In agreement with earlier data on CPGs in general,<sup>32</sup> Lacasse et al found that currently available guidelines for COPD were not evidence-based and probably reflected "the biases of selective experience rather than scientific knowledge."<sup>31</sup>

Lacasse and associates also found shortcomings in the clarity and readability of the guidelines. They pointed out that, while the ideal method for guideline development was uncertain, most would probably agree that explicitly stating each recommendation and identifying the level of evidence upon which it is based, using a standardized scheme, should be included. These authors also called for provision for regular updates to the guidelines, for specific attention to how the guidelines are to be implemented, and for investigation into the impacts of this implementation on clinical practice and patient outcomes.

In 1998, the National Heart, Lung, and Blood Institute and the World Health Organization convened a workshop to address the inconsistencies and shortcomings of previous COPD guidelines, as well as to develop strategies for wider guideline dissemination and implementation. Work-

shop participants adopted a formal evidence-grading scheme and applied it to a rigorous review of the literature on COPD. From this was developed an evidence-based report to serve as the foundation for the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Deliberate attempts were made to make GOLD truly global: the workshop's 20 panelists represented 11 different countries, and the document they generated was reviewed for input by 84 reviewers from 38 countries and 30 national and international professional societies. The full workshop report<sup>33</sup> was released in 2001, along with an executive summary, a pocket guide for clinicians, a teaching slide set, and some instructional materials for patients, which were made available free via the Internet at the GOLD Web site (<http://www.goldcopd.com>). The executive summary was also reprinted in *RESPIRATORY CARE*.<sup>34</sup>

In 2003, Smith et al<sup>35</sup> performed a systematic review of 6 COPD CPGs published by professional societies<sup>13,15,16,18,21,25</sup> plus the GOLD guidelines,<sup>33</sup> using independent assessments by 2 expert reviewers, according to 10 explicit criteria. These investigators echoed the concerns of Lacasse et al<sup>31</sup> about the lack of evidence-based guideline development, and found no evidence for methodologic improvement during the years prior to 2001. However, they scored the evidence-based GOLD CPG highest according to their 10-category, 3-point assessment scheme. Like Lacasse and colleagues, Smith et al pointed out the absence of data assessing the impact of published COPD guidelines on practice patterns or patient outcomes.

Smith and colleagues also included in their CPG assessment an evaluation of the funding sources for guideline preparation.<sup>35</sup> They found that 6 of the 7 reviewed guidelines were sponsored directly or indirectly by a single drug company, and that the seventh guideline (GOLD) was sponsored by multiple companies. They also found that little attention was paid to cost considerations in any of the guidelines, and that almost nothing was included about potential ethical implications or conflicts of interest with respect to funding for the guidelines.

### Currently Available Guidelines

A PubMed search in all languages for practice guidelines on COPD published between January 2000 and November 2005 yielded 51 citations. Most of these deal with managing exacerbations, oxygen therapy, or other specific topics. The 12 new or revised general CPGs include several international projects: an update of the GOLD guidelines,<sup>36,37</sup> a new CPG developed jointly by the ATS and the ERS,<sup>38-40</sup> an updated guideline from the Thoracic Society of Australia and New Zealand,<sup>41</sup> and a document from the Société de Pneumologie de Langue Française.<sup>42,43</sup> New or updated guidelines from

national professional societies and other country-specific groups are those of the Canadian Thoracic Society,<sup>44</sup> the Deutsche Atemwegsliga and Deutsche Gesellschaft für Pneumologie,<sup>45</sup> the Finnish Association of Pulmonologists,<sup>46</sup> the National Collaborating Centre for Chronic Conditions in Great Britain (in collaboration with the National Institute for Health and Clinical Excellence),<sup>47,48</sup> the Sociedad Española de Neumología y Cirugía Torácica (SEPAR),<sup>49</sup> the South African Thoracic Society,<sup>50</sup> the Swiss Respiratory Society,<sup>51</sup> and the World Health Organization/Government of India Biennium Programme.<sup>52</sup>

Among the CPGs published in the last 6 years, those most important to clinicians in the United States are from the ATS-ERS,<sup>38-40</sup> GOLD,<sup>36,37</sup> and the British National Collaborating Centre for Clinical Excellence (known as the NICE guidelines).<sup>47,48</sup>

The "Standards for the Diagnosis and Treatment of Patients With COPD" document,<sup>38</sup> published in 2004, combines and updates the position papers on COPD published by the ATS<sup>15</sup> and ERS<sup>16</sup> in 1995. Its authors cite a number of reasons for creating the new document. These include acknowledgment of the dissemination and impact of GOLD and the desire to establish a modular Web-based resource. Also stated were interests on the part of both societies to amplify what was in the initial GOLD initiative with respect to oxygen therapy, pulmonary rehabilitation, noninvasive ventilation, surgery in patients with COPD, sleep, air travel, end-of-life issues, and the control of smoking.<sup>38</sup> The ATS-ERS guideline is Web-based and consists of 2 components: a 15-page standards document for health professionals, aimed at raising awareness of COPD and summarizing recent advances, and a resource for patients, intended to provide information and promote a healthy lifestyle.

GOLD is a multifaceted initiative that works with health-care professionals and public health officials around the world to raise awareness of COPD and to improve prevention and treatment of this lung disease. The creation and promotion of evidence-based CPGs is only one of its activities, which also include World COPD Day (which will be November 15 in 2006), and associated newsletters and international events. Claude Lenfant, former director of the National Heart, Lung, and Blood Institute of the United States National Institutes of Health, recently became Executive Director for GOLD.

The original GOLD CPG<sup>33</sup> has been updated annually, starting in 2003,<sup>36</sup> and a more thorough revision is scheduled for release in 2006. The GOLD Web site<sup>37</sup> provides an extensive array of resources for health professionals, including a pocket guide "for physicians and nurses" and a downloadable teaching slide set, as well as documents intended for the public. The CPG itself is available as a 128-page full workshop report<sup>33</sup> and as a 33-page ex-

Table 2. Comparison of Spirometric Staging Criteria in the Current ATS-ERS, GOLD, and NCCCC-NICE Guidelines, Using FEV<sub>1</sub> As a Percentage of the Predicted Value\*

| Stage or Severity | FEV <sub>1</sub> Percent of Predicted |                    |                    |
|-------------------|---------------------------------------|--------------------|--------------------|
|                   | ATS-ERS <sup>38</sup>                 | GOLD <sup>36</sup> | NICE <sup>47</sup> |
| At risk for COPD  | ≥ 80                                  | ≥ 80               | †                  |
| Mild COPD         | ≥ 80                                  | ≥ 80               | 50–80              |
| Moderate COPD     | 50–80                                 | 50–80              | 30–49              |
| Severe COPD       | 30–50                                 | 30–50              | < 30               |
| Very severe COPD  | < 30                                  | < 30‡              | †                  |

\* All 3 guidelines define airflow obstruction as a criterion for diagnosing COPD as FEV<sub>1</sub>/forced vital capacity ≤ 0.70. Values for FEV<sub>1</sub> are post-bronchodilator.

† Stage not included in guideline.

‡ FEV<sub>1</sub> < 50% of predicted if chronic respiratory failure with P<sub>aO<sub>2</sub></sub> < 8.0 kPa (60 mm Hg) is also present.

ATS = American Thoracic Society

ERS = European Thoracic Society

GOLD = Global Initiative for Chronic Obstructive Lung Disease

NCCCC = National Collaborating Centre for Chronic Conditions

NICE = National Institute for Health and Clinical Excellence

FEV<sub>1</sub> = forced expiratory volume in the first second

COPD = chronic obstructive pulmonary disease

ecutive summary,<sup>34</sup> the latter with an appendix on outcomes and markers in COPD, both in portable document format (PDF).

The complete NICE guideline is a 232-page document published as a supplement to *Thorax* and is accessible free in PDF via *Thorax*'s Web site.<sup>47</sup> It can also be accessed via the NICE Web site,<sup>48</sup> along with its companion document for patients ("the public").<sup>53</sup>

### Content Comparison of the ATS-ERS, GOLD, and NICE Guidelines in Selected Areas

#### Diagnosis and Staging

All 3 guidelines identify airflow obstruction as the primary physiologic characteristic of COPD, including in their definitions the progressive nature of the obstruction over time and the fact that it is not fully reversible. All three also emphasize that, while symptoms and an appropriate exposure history are important in making the diagnosis of COPD, that diagnosis also requires the demonstration of airflow obstruction, via spirometry. The severity of this airflow obstruction, as measured by post-bronchodilator FEV<sub>1</sub>, is the primary factor used in determining the overall severity of the illness in a particular patient. While the criteria for spirometric severity and clinical staging differed among available guidelines a decade ago, the current ATS-ERS, GOLD, and NICE guidelines generally agree (Table 2).

The ATS-ERS and GOLD systems include 5 levels of severity, or stages, including a controversial "at risk" stage (stage 0 in GOLD) for individuals at risk for developing

COPD,<sup>54,55</sup> and a "very severe" stage (GOLD stage IV). While adopting the GOLD criteria for the different categories of severity, the ATS-ERS guideline distances itself from overt staging, observing that "a staging system that could offer a composite picture of disease severity is highly desirable, although it is currently unavailable." The British guidelines use only a 3-stage classification of mild, moderate, and severe, corresponding to ATS-ERS stages of moderate, severe, and very severe, and GOLD stages II, III, and IV. In the GOLD system, patients with FEV<sub>1</sub> values between 30% and 50% of predicted who are also chronically hypoxemic (P<sub>aO<sub>2</sub></sub> < 60 mm Hg) are advanced from stage III into stage IV.

#### Smoking Cessation

Discussions of the importance of smoking cessation and available approaches and therapies to facilitate it are included in all 3 guidelines. All emphasize the strength of the evidence base supporting smoking cessation while acknowledging the challenges involved in this aspect of management. The GOLD discussion is the most comprehensive and includes 6 figures or tables with algorithms and other guidance for helping patients to quit.

#### Pharmacologic Management of Stable Disease

A substantial proportion of each guideline is devoted to the use of drugs in patients with clinically stable COPD. Most comprehensive is the British guideline, which in the full document<sup>47</sup> devotes 67 pages to pharmacologic agents and their administration. In general, the recommendations of the 3 guidelines are the same, although GOLD is the most specific and prescriptive. All recommend escalation of drug therapy with increasing severity of disease, starting with short-acting inhaled bronchodilators used on an as-needed basis, proceeding to scheduled administration of long-acting inhaled bronchodilators, and finally advancing to inhaled corticosteroids in patients with severe or very severe disease with frequent exacerbations. All of them recommend combination therapy in patients with more severe disease. They advocate the use of metered-dose inhalers and dry powder inhalers for bronchodilator delivery, with nebulizers reserved for patients in whom these have been unsuccessful or cannot be used. All 3 guidelines acknowledge that theophylline is an effective bronchodilator but caution about its adverse effects and recommend adding its use only if other agents are unavailable or have been unsuccessful. All advise against the prolonged use of prednisone and other systemic corticosteroids.

Differences among the recommendations exist but are relatively minor. None of the current guidelines specifies which type of bronchodilator— $\beta$  agonist or anticholinergic—should be tried first for either short- or long-acting

therapy, and all state or imply that individual patient response or preference should be taken into account. In all 3 guidelines, inhaled corticosteroids are recommended, but only for patients whose post-bronchodilator FEV<sub>1</sub> values are  $\leq 50\%$  of the predicted value and who have frequent exacerbations; NICE defines the latter as  $\geq 2$  exacerbations in the last year; GOLD uses  $\geq 3$  episodes in the last 3 years; and the ATS-ERS guideline does not specify an exacerbation frequency. All of the guidelines caution that courses of systemic corticosteroids to determine which patients will benefit from inhaled corticosteroids have been shown not to be effective and should not be used. The NICE guideline points out that inhaled corticosteroids are not approved by the National Health Service for use in COPD, so its recommendation is off-label; NICE is also less emphatic than the other 2 guidelines in proscribing the long-term use of prednisone in patients with COPD.

For many years, mucolytic agents and antioxidants have been used in some areas (particularly in parts of Europe, Asia, and Africa) in the treatment of patients with cough and sputum, and all 3 guidelines address these drugs. Although mucolytic therapy is not mentioned in the ATS-ERS summary publication,<sup>38</sup> it is discussed on the Web sites of both parent organizations.<sup>39,40</sup> Citing a Cochrane collaborative review and meta-analysis that found a significant reduction in exacerbations with the use of mucolytic agents,<sup>56</sup> the ATS-ERS guidelines also refer to an ongoing multicenter clinical trial of N-acetylcysteine, but makes no recommendation. In stating that “the widespread use of these agents cannot be recommended,” GOLD cites the same evidence base as ATS-ERS, cautions that existing studies are suboptimal, and notes that “the overall benefit seems to be very small.”<sup>37</sup> Previously unavailable in Britain via the National Health Service, mucolytic therapy “should be considered in patients with a chronic cough productive of sputum,” with continuation of the therapy if symptoms are improved, according to the NICE guideline.<sup>47,48</sup>

### **Pulmonary Rehabilitation**

On the subject of pulmonary rehabilitation, there is agreement. All 3 guidelines strongly endorse pulmonary rehabilitation as an important component of COPD management, not only for end-stage disease but also for patients with less severe COPD. The GOLD and NICE guidelines each devote about 3 pages to this topic, summarizing the evidence supporting pulmonary rehabilitation and describing its components and multidisciplinary nature. Both GOLD and NICE discuss costs and benefits. The ATS-ERS summary document<sup>38</sup> has less than 1 page on the topic but recommends rehabilitation for all patients with substantial symptoms and impact on quality of life. Both the ATS-ERS and NICE guidelines emphasize that candi-

dates for rehabilitation should be chosen because of symptoms rather than according to any FEV<sub>1</sub> or other physiologic criterion.

### **Long-Term Oxygen Therapy**

Although the guidelines mainly agree with respect to long-term oxygen therapy, there are some differences (Table 3). All three state that long-term oxygen therapy (LTOT) is indicated for patients whose P<sub>aO<sub>2</sub></sub> is  $< 55$  mm Hg (7.3 kPa), although only the NICE guideline requires an arterial blood gas sample, as opposed to a saturation measurement. For patients with less severe hypoxemia, evidence of secondary end-organ dysfunction is required. Signs of pulmonary hypertension, peripheral edema, and secondary erythrocytosis are accepted for this by all 3 guidelines; NICE<sup>47</sup> also accepts nocturnal desaturation, and ATS-ERS<sup>38</sup> also mention impaired mental status as an acceptable criterion. GOLD<sup>36</sup> does not specifically mention the need to demonstrate clinical stability in qualifying patients for LTOT, while the others do.

“Short-burst” oxygen inhalation for the symptomatic relief of dyspnea in nonhypoxemic patients is widely prescribed by general practitioners in the United Kingdom, and while both the GOLD and NICE guidelines point out the lack of evidence supporting this practice, neither goes so far as to say it should be discontinued. While acknowledging the prevalence of “short-burst” use, the NICE guideline also strongly cautions against “uncontrolled oxygen therapy” in COPD because of the risk for respiratory-drive depression, carbon dioxide narcosis, and death. GOLD does not mention the potential for suppressing ventilatory drive when oxygen is administered. The ATS-ERS guideline does not mention “short-burst” oxygen therapy, and comments that reversal of hypoxemia supersedes any concerns about suppressing ventilatory drive.

Provision is made for ambulatory oxygen therapy in all 3 guidelines, for patients who have correctable desaturation during exercise and who wish to have it, although in the NICE guideline only a specialist may prescribe it.

### **Patient Materials**

Through their Web sites, all 3 CPGs provide materials for patients, although these differ substantially with respect to content, format, and detail. The ATS-ERS guideline includes documents for patients addressing most of the same topics covered in the main guideline. The materials are accessed differently via the ATS<sup>39</sup> and ERS<sup>40</sup> Web sites, but they are essentially the same. Approximately 30 documents are linked under headings labeled “General,” “Medications,” and “Other Treatments.” These range from a single paragraph to discussions several pages in length, and although there are a few diagrams in the

## REVIEW AND COMPARISON OF COPD PRACTICE GUIDELINES

Table 3. Selection Criteria for Long-Term Oxygen Therapy in Current COPD Guidelines

| Criterion   | ATS-ERS <sup>38</sup>  | GOLD <sup>36</sup>  | NCCCC-NICE <sup>47</sup>  |
|---|--|---|---|
| Demonstration of clinical stability                                 | ABG repeated in 30–90 d if initially assessed during exacerbation  | Not mentioned   | 2 ABGs at least 3 weeks apart   |
| ABG or S <sub>pO<sub>2</sub></sub> for assessing oxygenation?       | ABG preferred  | Either  | ABG required  |
| Oxygenation threshold for LTOT without need for additional criteria | P <sub>aO<sub>2</sub></sub> < 7.3 kPa (55 mm Hg)   | P <sub>aO<sub>2</sub></sub> < 7.3 kPa (55 mm Hg) or S <sub>pO<sub>2</sub></sub> ≤ 88%   | P <sub>aO<sub>2</sub></sub> < 7.3 kPa   |
| Criteria for LTOT with less severe hypoxemia                        | P <sub>aO<sub>2</sub></sub> 7.3–7.8 kPa plus at least one of:<br>P pulmonale<br>Hematocrit > 55%<br>History of edema<br>Impaired mental status | P <sub>aO<sub>2</sub></sub> 7.3–8.0 kPa (55–59 mm Hg) plus at least one of:<br>Pulmonary hypertension<br>Peripheral edema<br>Hematocrit > 55% | P <sub>aO<sub>2</sub></sub> 7.3–8.0 kPa plus at least one of:<br>Pulmonary hypertension<br>Peripheral edema<br>Secondary polycythemia<br>Nocturnal desaturation (S <sub>pO<sub>2</sub></sub> < 90% more than 30% of the time) |
| Criteria with P <sub>aO<sub>2</sub></sub> > 8.0 kPa (60 mm Hg)      | Exercise desaturation<br>Sleep desaturation not corrected with CPAP<br>Lung disease with severe dyspnea that responds to oxygen                | “Short burst” oxygen for dyspnea discussed but no recommendation given  | “Short burst” oxygen for dyspnea discussed but no recommendation given  |
| Goals of therapy  | Maintain S <sub>pO<sub>2</sub></sub> > 90% during rest, sleep, and exertion  | S <sub>pO<sub>2</sub></sub> > 90%<br>Use for at least 15 h/d  | No S <sub>pO<sub>2</sub></sub> target given<br>Use for at least 15 h/d  |
| Type of stationary system in home                                   | No recommendation  | No recommendation<br>“Concentrator more cost-effective than cylinders”  | Concentrator  |
| Ambulatory oxygen   | For active patients  | “Where available” for patients who meet the criteria for continuous oxygen or who experience substantial desaturation during exercise         | For patients already on LTOT who desire it<br>For patients who desaturate on exercise, whose exercise capacity and/or dyspnea is improved<br>Only on the recommendation of a specialist                                       |

COPD = chronic obstructive pulmonary disease  
 ATS = American Thoracic Society  
 ERS = European Thoracic Society  
 GOLD = Global Initiative for Chronic Obstructive Lung Disease  
 NCCCC = National Collaborating Centre for Chronic Conditions  
 NICE = National Institute for Health and Clinical Excellence  
 ABG = arterial blood gas measurement  
 S<sub>pO<sub>2</sub></sub> = oxyhemoglobin saturation measured via pulse oximetry  
 LTOT = long-term oxygen therapy  
 CPAP = continuous positive airway pressure

document on anatomy and function of the lungs, they consist mainly of text. Because the CPG is intended for an international readership, the ATS-ERS materials contain information on many medications and devices that are unfamiliar (and unavailable) to American patients.

Patient materials at the ERS Web site are in the form of brief summaries, with links to a more comprehensive, printable version, whereas the ATS site displays the full-text

version. The documents at the ERS Web site are available in English, French, German, Italian, and Spanish; they are translations of the same text, except that the German version omits some illustrations present in the others.

Resources for patients at the GOLD Web site consist of links to a brief description of COPD and an interactive questionnaire to determine the visitor's likelihood of having it, plus a patient guide in the form of a PDF file to download.

This 20-page guide<sup>57</sup> describes COPD and its management, using elementary language and simple cartoon illustrations. It does not contain information about specific medications or other modalities. The guide is in English, although an Italian version can be accessed via the Web site.

Patient materials in connection with the NICE guideline consist of a 56-page booklet.<sup>53</sup> The latter is all text (no diagrams or other illustrations) and covers most of what is addressed in the full guideline. It is intended for use in the United Kingdom's National Health Service system, and is available in English and Welsh.

### End-of-Life Issues

Advance care planning and end-of-life care are treated variably in the guidelines. GOLD contains no mention of advance care planning or end-of-life care in its executive summary, pocket guide, or patient materials. In the GOLD full workshop report, these subjects are not addressed in the section on managing stable disease; when discussing the decision to intubate in the section on in-hospital management of exacerbations, it says only that "when possible, a clear statement of the patient's own treatment wishes—an advance directive or 'living will'—makes these difficult decisions much easier to resolve."<sup>37</sup>

Although I was unable to find anything on end-of-life care in the sections of the ATS-ERS guideline for physicians and other clinicians, there is a discussion of this topic in the patient section of the Web site, primarily focused on encouraging patients to discuss end-of-life preferences with their providers.

Section 7.20.5 of the NICE guideline is devoted to palliative care.<sup>47</sup> In several text pages it reviews published evidence on the use of opioids and other drugs for the control of dyspnea, patient attitudes toward end-of-life decision making, and the attitudes of physicians about discussing the end of life with their patients. In Appendix C of the NICE guidelines,<sup>47</sup> which is on educational packages to be made available to COPD patients, information on advance directives is included in the list of recommended contents. Two of the 3 specific guideline recommendations pertaining to end-of-life care deal with the use of drugs for breathlessness; the third states that patients and family members should have access to the full range of services offered by multidisciplinary palliative care teams, including hospice care.

### Critique

The generation of COPD CPGs that appeared during the 1990s consisted of expert-opinion-based consensus recommendations developed more or less independently by professional societies and other groups. Not surprisingly, given their diverse origins and the paucity of definitive

studies to determine the best approaches and therapies, these CPGs, while generally agreeing with respect to areas of emphasis and overall approach, differed from one another in important ways. In revising this first generation of CPGs and developing the new ones released in the last 5 years, issuing groups have been able to use the older documents for comparison and also to respond to criticisms of their methods and recommendations.<sup>30,31,35</sup> As a result, current CPGs—particularly the three reviewed in most detail in this article<sup>36,38,47</sup>—are much more consistent with one another than were their predecessors.

### Evidence-Based?

Previous CPGs were criticized for not using formal methods to establish the levels of evidence used in making their recommendations.<sup>31,35</sup> GOLD<sup>36</sup> was the first major guideline to use an explicit evidence classification system and to refer to this in each of its recommendations. The ATS and ERS<sup>38</sup> did not perform a separate examination of the evidence, but instead used the GOLD evidence base as the foundation for their recommendations, which are more an embellishment of the GOLD recommendations than a new system. The NICE guideline<sup>47</sup> uses a different evaluation system but explicitly states the evidence base in every subject it covers and relates each recommendation to this. Thus, for these 3 main guidelines in English, previous methodologic criticisms have been addressed, and the requirements of evidence-based CPGs have been fulfilled.<sup>4</sup>

### Target Audience

All 3 guidelines contain materials for health professionals and also for patients and other members of the public. The documents and resources for physicians and other health professionals differ somewhat in structure and comprehensiveness, but are presented in a manner appropriate for primary care providers. The ATS-ERS summary document<sup>38</sup> is the most concise and accessible of the resources of the 3 CPGs from the perspective of the respiratory specialist. A project of the World Health Organization as well as of the United States National Institutes of Health, GOLD is deliberately and explicitly a worldwide initiative. The ATS-ERS guideline is also international in its scope, aimed at the memberships of the 2 societies. In contrast, the NICE guideline is a project of the National Health Service and targeted at British physicians and their patients. These differences in intended audience led to some differences between the guidelines, despite their similarity in scope and subject matter.

### Provision for Frequent Updating

The previous generation of COPD CPGs consisted of specific documents prepared by their respective profes-

sional groups for publication on a particular date. In general there was no built-in mechanism for revision or updating, and subsequent versions were approached on an as-needed basis. In contrast, the GOLD project included provisions for repeating the literature search and posting updates on a regular basis. Such updates were issued in 2003,<sup>36</sup> 2004, and 2005, with a more complete revision planned for release in 2006. Although the core guidelines of ATS-ERS and NICE are discrete documents, their Web-focused presentation should also assure the timely posting of updated information and resources.

### Accessibility and User-Friendliness

Having the documents and other materials accessible free on the Web makes the current CPGs more readily available than their predecessors. The Web sites of all 3 CPGs are fairly straightforward for those who are familiar with navigating the Internet. The ATS-ERS guideline is accessible via the individual Web sites of its parent societies, which are somewhat different in terms of layout and linking to the individual elements. GOLD's Web site is the most elaborate, professional, and user-friendly.

All 3 CPGs make reference to pharmaceutical agents and brand names that are unavailable in the United States, and patients accessing some of the materials could find this confusing. In discussing oxygenation and listing criteria for oxygen therapy, the GOLD and ATS-ERS guidelines use both *Système Internationale* units (kilopascals, kPa) and mm Hg, whereas all references to blood gas tensions in the NICE CPG are in kPa only, emphasizing the fact that the NICE guideline is intended for British practitioners and making it less accessible for those in North America.

### Applicability to Different Health Care Systems and Patient Populations

The multicultural character of society is increasingly evident every day. However, guideline development has given little attention to this fact. In their evaluation of CPGs from the 1990s, Lacasse et al noted that, "with few exceptions, there was no clear indication that local and cultural influences had modulated any of the organizations' recommendations."<sup>31</sup> They further stated that "even well-conducted systematic reviews are insufficient for guidelines until they are interpreted in the context of local factors, such as patient preferences and the health care setting in which the recommendations are being made."<sup>31</sup>

Lacasse and associates used pulmonary rehabilitation as an example, citing the very small proportion of COPD patients to whom this modality is available worldwide. A study by Brooks et al found that, in the late 1990s, fewer than 2% of Canadians had access to a pulmonary rehabil-

itation program.<sup>58</sup> The 1997 BTS guidelines also noted the very limited availability of rehabilitation programs in the United Kingdom, despite their recommendation that such programs be used in patients with COPD.<sup>21</sup>

The potential gulf between what is recommended in the guidelines and what can practically be achieved is especially apparent in developing countries. Despite its international authorship and avowed global aim, GOLD makes recommendations that are problematic for a substantial fraction of the world's COPD patients and the health systems that serve them. Chan-Yeung et al evaluated GOLD's applicability for managing COPD in Asia and Africa, and made a number of observations.<sup>59</sup> First, cigarette sales are burgeoning in the developing world, making the need for greatly augmented measures for tobacco prevention and control especially acute. Second, for countries with a high prevalence of infectious diseases such as tuberculosis and acquired immune deficiency syndrome, the control and management of COPD are low priority, if they are on the "radar screen" at all. Third, in many countries, the emphasis on spirometry as the cornerstone of diagnosis and staging in GOLD and the other guidelines essentially precludes their intended implementation for the huge numbers of patients without access to the few centers that offer spirometry. Chan-Yeung and colleagues point out that in these settings clinicians need to rely more heavily on clinical signs, and they provide a table from the 1997 BTS guidelines that attempts to link symptoms and physical signs with different degrees of airflow obstruction.<sup>21</sup>

Although the guidelines stress continuing care in patients who are clinically stable, the reality is that many patients in underserved regions have contact with the health-care system only during times of severe acute illness.<sup>59</sup> The pharmacologic agents recommended for the guidelines' progressively escalating therapy with increasing disease severity—such as long-acting bronchodilators and inhaled corticosteroids—have only limited availability in many areas, and patients may have access only to theophylline, oral  $\beta$  agonists, and oral corticosteroids. A number of the therapies recommended by the guidelines, including alpha-1 antitrypsin replacement therapy, lung-volume reduction surgery, and even LTOT, are simply unavailable to large numbers of the world's COPD patients. In addition, for regions with a high prevalence of tuberculosis, human immunodeficiency virus, and other chronic infections, the safety of long-term, high-dose inhaled corticosteroids has not been established with certainty.

A consensus group of expert pulmonologists from 9 countries in the Asia-Pacific region also published recommendations for adapting the GOLD CPG for areas of limited health-care resources.<sup>60</sup> They supported the GOLD recommendations but noted the need for a number of modifications. These included the use of the history and physical signs for diagnosis and staging when spirometry is not

## REVIEW AND COMPARISON OF COPD PRACTICE GUIDELINES

Table 4. Potential Monthly Costs for Recommended Therapy for Patients With Stable COPD\*

| Disease Severity                                   | Agent  | Brand Name (Manufacturer)  | Cost (\$) | Total (\$) <sup>†</sup> |
|--|--|--|-----------|-------------------------|
| <b>Mild COPD (GOLD Stage I)</b>                    |  |  |           |                         |
| Short-acting bronchodilator as needed <sup>‡</sup> | Albuterol                                    | Generic  | 15.00     |                         |
|  | Albuterol                                    | Proventil HFA (Schering-Plough)                                      | 42.20     |                         |
|  | Ipratropium                                  | Generic <sup>§</sup>   | 51.75     |                         |
|  | Ipratropium                                  | Atrovent HFA (Boehringer-Ingelheim)                                  | 66.85     |                         |
|  | Both albuterol and ipratropium (generics)    |  | 66.75     |                         |
|  | Both albuterol and ipratropium (brand names) |  | 109.05    | 109.05                  |
| <b>Moderate COPD (GOLD Stage II)</b>               |  |  |           |                         |
| Add regular long-acting bronchodilator             | Salmeterol                                   | Serevent Diskus (GlaxoSmithKline)                                    | 100.16    |                         |
|  | Tiotropium                                   | Spiriva Handihaler (Boehringer-Ingelheim)                            | 115.20    |                         |
|  | Both   |  | 215.36    | 324.41                  |
| <b>Severe COPD (GOLD Stage III)</b>                |  |  |           |                         |
| Add inhaled corticosteroid                         | Fluticasone                                  | Flovent HFA <sup>  </sup> (GlaxoSmithKline)                          | 142.58    | 466.99                  |
| <b>Very Severe COPD (GOLD Stage IV)</b>            |  |  |           |                         |
| Add long-term oxygen therapy                       | Oxygen                                       | Medicare reimbursement rate for both stationary and portable systems | 266.36    | 733.35                  |

\* The medication costs are average wholesale price (AWP)<sup>62</sup> using 2005 pricing. The Medicare reimbursement rate for long-term oxygen therapy (LTOT) is from the Department of Health and Human Services, using 2002 data.<sup>61</sup> Where more than one product is available in a given drug category, a single representative brand widely used in the United States is shown.

<sup>†</sup> Total represents cumulative cost, assuming only brand name drugs are used and also assuming that all therapy from stage above is carried over to each new stage.

<sup>‡</sup> Cost computed assuming one metered-dose inhaler used per month

<sup>§</sup> Metered dose spray

<sup>||</sup> Assumes 220 µg/inhalation dose used; not FDA-approved for use in COPD as of 2005.

GOLD = Global Initiative for Obstructive Lung Disease<sup>36</sup>

HFA = hydrofluoroalkane

available; acknowledgment that oral bronchodilators may have to be used because of cost considerations, despite their less favorable therapeutic index than inhaled agents; the statement that using metered-dose inhalers with spacers (even home-made versions) is preferred over powered nebulizers; the recommendation that widespread influenza vaccination be used in areas that have the potential for epidemics of severe acute respiratory syndrome; and the implementation of simplified rehabilitation programs where full, formal programs are unavailable.

Costs and resource availability are problems for full implementation of the COPD guidelines in developed countries as well. Through its Medicare program, LTOT cost the United States government \$2.2 billion in 2002.<sup>61</sup> Monthly reimbursement to oxygen suppliers and home-care companies for each LTOT patient averages \$230.17 for a stationary system (regardless of the delivery system used) and \$36.19 for a portable system (again, irrespective of the devices used), for a total of \$266.36 per month.<sup>61</sup> Obviously, not all health-care systems could afford this.

Table 4 presents examples of current possible costs to patients with COPD for bronchodilators, inhaled corticosteroids, and LTOT in the United States.<sup>61,62</sup> Drug costs in the table are average wholesale prices for 2005,<sup>62</sup> and are less than patients without insurance would pay at many retail pharmacies. These potential costs for managing COPD according to the guidelines, which exceed \$700 per month for patients with GOLD stage IV disease, do not include those for other recommended therapies such as smoking cessation, immunizations, theophylline, antibiotics, and rehabilitation. In following the GOLD recommendations for sequentially escalating therapy with more severe disease, the table includes fluticasone to illustrate the incremental cost of adding inhaled corticosteroids. This agent is not currently approved by the United States Food and Drug Administration for treating COPD, however, except as combined with salmeterol (Advair Diskus 250/50, GlaxoSmithKline). Using the combined preparation instead of its components individually would reduce the monthly cost shown in the table by approximately \$100.<sup>62</sup> Most

American patients do not pay as much as shown in the table, but this exercise illustrates the substantial financial aspect of managing COPD.

### Summary

CPGs for COPD have evolved positively since their introduction 30 years ago. The ATS-ERS,<sup>38</sup> GOLD,<sup>36</sup> and NICE<sup>47</sup> guidelines, those currently most relevant to American clinicians, are explicitly evidence-based and agree in most areas. Although there are differences among them with respect to diagnostic criteria and recommended therapies, these are substantially fewer and less important clinically than those present in the CPGs of the 1990s. The ready accessibility of these guidelines via the Internet, and their inclusion of potentially helpful information for patients, should promote wider awareness and implementation. Full implementation of the recommendations in the guidelines is beyond the reach of many patients in developing countries and underserved areas elsewhere, although it can be hoped that this gap will diminish with time.

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