

Guidelines for Chronic Obstructive Pulmonary Disease Treatment and Issues of Implementation

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Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. Treatment advances over the last decade, although limited, have precipitated the development of clinical practice guidelines, with the aim of improving the quality of care received by patients through fostering evidence-based decision making and accelerating the application of new advances to everyday practice. Of the COPD guidelines that have been developed, those developed through the Global Initiative for Chronic Obstructive Lung Disease (GOLD), initially a joint activity between the U.S. National Heart, Lung, and Blood Institute and the World Health Organization, and the National Institute of Clinical Excellence (NICE) in the United Kingdom have both published their methods for evaluation of evidence. These comprehensive guidelines cover all aspects of the disease, with the aim of providing the basis for local care pathways. The guideline development process includes evaluation of the evidence, development of the guideline, and dissemination of the findings. Efforts to enhance guideline effectiveness have focused on improving the methods and approaches to implementation, which requires an appreciation of the issues that stop translation of guideline definitions of best practice into improved patient care. A variety of questions remain unanswered in the clinical management of COPD, including the definition of outcome measures that move beyond lung function, the potential application of multidimensional grading systems that assess respiratory and systemic expressions of COPD and that could possibly better categorize and predict outcome in these patients, and the impact of new clinical trial findings. Large ongoing outcome studies may also have an effect on defining best practice within future guideline recommendations.

Keywords: chronic obstructive pulmonary disease; guidelines

Chronic obstructive pulmonary disease (COPD), the fifth leading cause of global morbidity (1), is a major public health problem. In the past, management and treatment options for COPD were largely ignored because interventions to improve morbidity, mortality, and quality of life were lacking. However, over the last decade, substantial progress has been made in the interventions available, including developments in long-acting bronchodilator drugs and improved ventilation methods, and, reflecting the general shift in medicine toward evidence-based practice, there was recognition that improved, comprehensive management guidelines to evolve and optimize COPD patient care would be valuable (2). Although COPD guidelines have been developed and reported by major national bodies for the last 15 years (2, 3), most failed to meet important criteria for high-quality guideline development, and their impact on clinical care has largely been unknown (4). A critical appraisal of guidelines published before

2001 (5) concluded that COPD guidelines were limited by their methodologic quality and by discrepancies among the guidelines published by various professional groups.

Central to an improvement in the development of guidelines for COPD over the last 5 years has been the formation of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2000, starting as a joint activity between the U.S. National Heart, Lung, and Blood Institute and the World Health Organization and made up from experts in the fields of respiratory medicine, epidemiology, socioeconomics, public health, and health education. The central objectives of GOLD are to increase awareness of COPD and to help patients with COPD, and comprehensive guidelines were described for the first time by the GOLD initiative (2). More recently, the American Thoracic Society and the European Respiratory Society unveiled new COPD guidelines that have been jointly developed by the two organizations (3), and the National Institute of Clinical Excellence (NICE) in the United Kingdom set out to define a guideline "defining best practice advice on the identification and care of patients with COPD" (6). Both GOLD and NICE are particularly comprehensive guidelines that cover all aspects of the disease, with the aim of providing the basis for local care pathways. Gaps in the clinical evidence base have been filled by best-practice recommendations based on consensus among the experts (7).

In this review, the process of guideline development, including evidence evaluation in the GOLD and NICE guidelines, is described. The dissemination of guidelines and the barriers to implementation of guidelines are reviewed, and finally, the outstanding questions in clinical management, including the impact of large ongoing outcome studies may potentially have on the guideline recommendations, are examined.

COPD GUIDELINE DEVELOPMENT

A key principle at the heart of the guideline development process is transparency—in the steps undertaken to create the guidelines, in detailing the individuals involved, and in the definition of the recommendations that arise. Each of these elements has been adopted in the published GOLD and NICE guideline development process, described in more detail below.

The GOLD Science Committee Process

The GOLD program first began with the preparation of a consensus workshop report, "Global Strategy for the Diagnosis, Management, and Prevention of COPD," first published in 2001 (2) and based on the scientific knowledge up to mid-2000. The evidence is assigned a category from randomized controlled trials (Category A) to cases where the provision of some guidance is deemed valuable but the clinical literature addressing the subject was deemed insufficient to justify placement in one of the other categories (Table 1). This is given a Category D, and the panel consensus is based on clinical experience or knowledge that does not meet the criteria for high evidence. This approach is very similar across medicine, but has a principal limitation in that strong observational data are weakly graded, with the strongest grading reserved for randomized controlled trial data.

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TABLE 1. DESCRIPTION OF LEVELS OF EVIDENCE IN GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE

Evidence Category	Sources of Evidence	Definition
A	RCTs. Rich body of data.	Evidence is from endpoints of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
B	RCTs. Limited body of data.	Evidence is from endpoints of intervention studies that include only a limited number of patients, <i>post hoc</i> or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C	Nonrandomized trials Observational studies	Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.
D	Panel consensus judgment	This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was deemed insufficient to justify placement in one of the other categories. The panel consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.

Definition of abbreviation: RCT = randomized controlled trial.
Data from Reference 2.

To ensure that the recommendations for management of COPD remain as current as possible, the GOLD executive committee established two subcommittees: a dissemination committee and a science committee. It is the responsibility of the science committee to ensure that the guidelines remain up to date with published research and, to this end, post an updated report yearly on the GOLD website (www.gold.copd.org). The literature review and the process of recommending proposed modifications follow a structure. Every 3 months, a formal Pub Med search is conducted using the criteria established by the committee: (1) COPD OR chronic bronchitis OR emphysema, All Fields, All Adult, 19+ years, only items with abstracts, Clinical Trial, Human, sorted by Authors; and (2) COPD OR chronic bronchitis OR emphysema AND systematic, All fields, All adult, 19+ years, only items with abstracts, Human, sorted by Author. In addition, publications in peer review journals not captured by Pub Med can be submitted to individual members of the committee and new Cochrane or Systematic Reviews are included.

Committee members receive a summary of citations, with abstracts of all studies identified. Each abstract is evaluated specifically by two committee members who are not authors of the paper by answering set questions and are then asked to indicate if the scientific data presented impact on the recommendations. These include the following:

- Do the data have an impact on the GOLD report? If they do not, do not proceed, but please provide explanation why not.
- Do the data modify one or more GOLD recommendations/statements? If so, what specifically needs to be modified and why.

- Do the data confirm a GOLD recommendation/statement? If so, identify the GOLD recommendation/statement to which the data contribute.
- If the data add a new piece of information, not already in the GOLD report, what should be added to the report?

In this way, the reviewers identify the modifications that should be made. The summary comments are collated, returned to the Chair of the science committee and as new findings impact on GOLD recommendations, steps are taken to review the findings and post changes on the GOLD website. There are a number of criteria under which the changes fall and different actions that follow depending on the criteria. Errors in the workshop report/reference are reviewed by the Chair, science committee, and posted on the website under tab "errata" or "new reference." The addition of words to the text is reviewed by the Chair and the full science committee (plus other experts, if appropriate), and a posting on the website made as a text edit. As an example, between January 1 and December 31, 2004, 131 articles met the search criteria. Of these, 10 papers were identified to have an impact on the GOLD report, of which 5 papers confirmed an existing statement and were added as a reference.

The first (2003) and second (2004) updates were posted on the GOLD website in July 2003 and July 2004, respectively. The current update was posted in July 2005 and includes review of publications from January to December 2004. A decision has been made that this represents the final update of the 2001 document and revision of the entire document is scheduled for completion in 2006.

NICE GUIDELINE DEVELOPMENT: HIERARCHY OF EVIDENCE AND GRADING OF RECOMMENDATIONS

The NICE conducts technology appraisals and issues clinical guidelines in the United Kingdom. With respect to COPD, the remit was to prepare clinical guidelines for the National Health Service (NHS) in England and Wales for its prevention, diagnosis, management, and treatment.

The NICE process follows a highly structured and detailed development process, which is described in detail in the documents (6). Developers include a technical team (an information scientist, a systematic reviewer, a lead clinical advisor, and a health economist, supported by project management and administrative personnel), a guideline development group, a consensus reference group, and patient representation. A structured search is conducted, and there is an extensive drafting process followed by agreeing on recommendations and, finally, writing the guideline.

The NICE guideline differs from GOLD in a number of ways. There is a different approach to grading recommendations, with NICE translating a hierarchy of evidence to a grading recommendation (Table 2). The hierarchy of evidence and the recommendation grading relate to the strength of the literature, not to clinical importance. Furthermore, the NICE guidelines place stronger emphasis on the weighting of systematic reviews.

COPD GUIDELINES AND IMPLEMENTING PRACTICE CHANGE

Guideline implementation has been defined as a persistent process of communicating guideline recommendations by multiple and overlapping avenues and media that clinicians find hard to ignore as they perform their daily clinical tasks (8). Although the GOLD guideline development process has had a dissemination committee, which formed an equal part of the process as the guideline development efforts began, many guidelines do not impact on clinician behavior (4, 9, 10), and most guideline developers neglect to design implementation strategies as part of the

TABLE 2. HIERARCHY OF EVIDENCE AND GRADING OF RECOMMENDATIONS IN NATIONAL INSTITUTE OF CLINICAL EXCELLENCE

Level	Type of Evidence	Level	Type of Evidence
Ia	Evidence from systematic reviews or meta analysis of randomized controlled trials	A	Based on hierarchy I evidence
Ib	Evidence from at least one randomized controlled trial		
IIa	Evidence from at least one controlled study without randomization	B	Based on hierarchy II evidence or extrapolated from hierarchy I evidence
IIb	Evidence from at least one other type of quasi-experimental study		
III	Evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies	C	Based on hierarchy III evidence or extrapolated from hierarchy I or II evidence
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities	D	Directly based on hierarchy IV evidence or extrapolated from hierarchy I, II, or III evidence
NICE	Evidence from NICE guidelines or Health Technology Appraisal program	NICE	Evidence from NICE guidelines or Health Technology Appraisal program
HSC	Evidence from HSCs	HSC	Evidence from HSCs

Definition of abbreviations: HSC = Health Service Circular; NICE = National Institute of Clinical Excellence. Data from Reference 6.

guideline development process. Indeed, a recent survey showed that, although most physicians believed that proper treatment can slow progression in COPD, inadequate knowledge and poor adherence to practice guidelines, together with insurance impediments, negatively impacted COPD care (11). Other key issues are perceived failures within the guideline development process in terms of the systematic appraisal of the literature, and the guideline dissemination approach adopted.

Disseminating guidelines requires an appreciation of the issues that stop translation of guideline definitions of best practice into improved patient care. The whole implementation process requires careful consideration of whom the guidelines are written for, by whom they are written, the quality of the writing, and their relevance to the patient population. Failure to be transparent in terms of potential conflict of interest with respect to the expert preparing the guideline or the body funding the development process can be a valid criticism. The presentation of the guideline in clear, actionable language can have great benefits for dissemination. Similarly, the preparation of patient guidelines for a chronic disease like COPD can assist in improving patient disease understanding and medication compliance.

A practical example of implementation is the basis for lung function measurements. If we believe spirometry is important for classification of the severity of the disease, there is a need to consider spirometry in the primary care setting. Issues with adopting this approach include the limited knowledge and experience of primary care specialists with using spirometry and the sparse training they receive in medical school or during residency programs. Furthermore, spirometry has traditionally been the "territory" of academic pulmonary departments, and there is an impression of lack of data on sensitivity, and uncertainty over interpretation of the results. Therefore, implementing something we believe is simple has barriers to overcome and correct in the community, and this is coupled with other issues, including the training of staff, the need for quality assurance, patient acceptance, and the cost and reimbursement for these tests.

OUTSTANDING QUESTIONS IN CLINICAL MANAGEMENT OF COPD

A variety of questions remain unanswered in the clinical management of COPD, from obviously challenging issues, such as how

to predict mortality, to more achievable goals, such as defining composite measures of disease beyond simple FEV₁ measurement. There is great interest in the definition of outcome measures that move beyond lung function (12). Although lung function measurements are undertaken routinely in patients suspected of COPD, and spirometric tests are the gold standard for diagnosis because of high levels of reproducibility and availability, it is accepted that they measure a very limited aspect of the impact of COPD on a patient's health (13). The definition of other parameters that could be monitored by functional measurements may have value, and suggestions include disease progression, the effects of drug interventions, and progress of rehabilitation, which could potentially be assessed by measuring hyperinflation, residual volume, and inspiratory capacity (14, 15). However, it is the potential application of multidimensional grading systems that assess respiratory and systemic expressions of COPD and that potentially better categorize and predict outcome in these patients that have been a focus of interest over the last 2 years (16). Celli and coworkers constructed a multidimensional grading system, based on FEV₁, 6-minute walk test result, dyspnea assessment, and body mass index (16). They reported that this so-called BODE index was better than FEV₁ at predicting mortality. The effect of this is that future guidelines and treatment algorithms may have to move away from the commonly used staging system based on FEV₁ alone, especially with respect to mortality. In other words, more sophisticated staging of COPD is required to account for prognosis and potential response to different treatment strategies.

Defining clinical phenotypes in COPD is another area of interest. Clearly, the risk of developing COPD is dependent on the amount and duration of cigarette smoking, but there are significant differences in susceptibility between individuals. Although an individual's exposure to other risk factors is cumulative with those from tobacco smoke, this does not explain the differences between smokers in the rate of FEV₁ decline. The fact that severe deficiency for α_1 -antitrypsin places individuals at an increased risk of developing COPD supports this (17). Comorbidities are very important as we now recognize that COPD is a reflection of a systemic chronic inflammatory disorder that predisposes to a variety of vascular abnormalities. It is clear therefore that many unanswered questions remain in the

management of COPD, all of which will greatly influence guideline development over the next decade.

ONGOING OUTCOME STUDIES

Two large ongoing studies will be of particular interest for future guideline assessment. The TOWard a Revolution in COPD Health (TORCH), a randomized, double-blind, parallel-group, placebo-controlled study, which will report in 2006, aims to determine the impact of salmeterol/fluticasone propionate combination and the individual components on survival of patients with COPD (18). The study is taking place at multiple centers across the world, with approximately 6,200 patients with moderate to severe COPD having been randomly assigned to twice-daily treatment with either the salmeterol/fluticasone propionate (50/500 µg) combination, fluticasone propionate (500 µg) alone, salmeterol (50 µg) alone, or placebo for 3 years. The study is primarily a survival study with a primary endpoint of all-cause mortality.

In addition to the primary goal of assessing mortality, TORCH will also provide evidence on areas of controversy with respect to the long-term use of inhaled corticosteroids in COPD. Patients participating at several of the centers are undergoing annual bone mineral densitometry, slit lamp-eye examination, and assessment of cortisol secretion. Furthermore, there may be a possibility to genotype a proportion of the patients in the study. This may afford the opportunity to undertake more sophisticated genotype/phenotype analyses with respect to treatment response, outcome, and death, which may open new vistas in COPD research and treatment.

The Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study, another large, multicenter long-term trial, is investigating the long-term impact of tiotropium on lung function in up to 6,000 patients with COPD (19). The primary objective is to determine whether tiotropium reduces the rate of lung function decline (as measured by FEV₁) over time. Other outcome measures include quality of life, exacerbations, and mortality. The first UPLIFT results are expected in 2008.

Both of these large studies may result in a significant step forward in the pharmacologic management of COPD, on the basis that, besides smoking cessation and oxygen supplementation, no interventions have been shown to affect lung function decline and the progression of COPD. These two large outcome studies will obviously stimulate discussion and potentially influence future guidelines.

CONCLUSIONS

COPD clinical practice guidelines have evolved markedly over the last 5 years into rigorous, evidence-based, and graded assessments of the medical literature and are updated regularly. The GOLD and NICE guidelines both use a systematic approach to retrieving, grading, and synthesizing the primary evidence. A key feature of development of the GOLD and NICE guidelines has been transparency in detailing the individuals involved and in the background to the definition of the recommendations. Although a variety of questions remain unanswered in the clinical management of COPD, there is great interest in the definition of outcome measures that move beyond lung function. Recent developments have shown the potential benefits of composite endpoints using multidimensional grading systems that assess

respiratory and systemic expressions of COPD that potentially better categorize and predict outcome. The findings of the TORCH and UPLIFT studies are eagerly awaited, and will shed light on the use of inhaled corticosteroids, combination therapy, and long-acting bronchodilators and generate new hypotheses for improved COPD management in the 21st century.

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