

Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Summary and Appraisal of Published Evidence

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Purpose: To review critically the available data on diagnostic evaluation, risk stratification, and therapeutic management of patients with acute exacerbations of chronic obstructive pulmonary disease (COPD).

Data Sources: English-language articles were identified by searching MEDLINE (1966 to 2000, week 5), EMBASE (1974 to 2000, week 18), HealthStar (1975 to June 2000), and the Cochrane Controlled Trials Register (2000, Issue 1).

Study Selection: The best available evidence on each subtopic was selected for analysis. Randomized trials, sometimes buttressed by cohort studies, were used to evaluate therapeutic interventions. Cohort studies were used to evaluate diagnostic tests and risk stratification.

Data Extraction: Study design and results were summarized in evidence tables. Individual studies were rated by internal validity, external validity, and quality of design. Statistical analyses of combined data were not performed.

Data Synthesis: Data on the utility of most diagnostic tests are

limited. However, chest radiography and arterial blood gas sampling seem useful while acute spirometry does not. Identifiable clinical variables are associated with risk for relapse and risk for death after hospitalization for an acute exacerbation. Evidence of efficacy was found for bronchodilators, corticosteroids, and non-invasive positive-pressure ventilation. There is also support for the use of antibiotics in patients with more severe exacerbations. On the basis of limited data, mucolytics and chest physiotherapy do not seem to be of benefit, and oxygen supplementation seems to increase the risk for respiratory failure only in an identifiable subgroup of patients.

Conclusions: Although suggestions for appropriate management can be made on the basis of available evidence, the supporting literature is scarce and further high-quality research is necessary. Such research will require an improved, generally acceptable, and transportable definition of acute exacerbation of COPD, as well as improved methods for observing and measuring outcomes.

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The primary aims of this paper are 1) to summarize and evaluate published data that address care of patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) and 2) to improve the care that these patients receive by identifying efficacious and inefficacious treatment strategies. This paper provides the background evidence for the clinical practice guideline in this issue (see pages 595-599). A joint panel from the American College of Physicians–American Society of Internal Medicine (ACP–ASIM) and the American College of Chest Physicians (ACCP) assisted in the design, conduct, and development of this paper. The paper is based largely on the evidence report produced by the Evidence-Based Practice Center at Duke University, Durham, North Carolina, under contract with the Agency for Healthcare Research and Quality (AHRQ) (1). We review the health impact of COPD, define the

entity *acute exacerbation*, and describe the methods we used to identify and grade the available data on care of this condition. In addition, we assess studies that evaluate diagnostic techniques, prognostic and risk stratification models, and an array of therapies and interventions. In the concluding sections, we review important elements of postexacerbation management, with special attention to follow-up care, and gradual titration of such therapeutic agents as oxygen and corticosteroids. Last, we comment on areas of management for patients with acute exacerbations that would most benefit from further research.

In the United States, more than 16 million adults have COPD, a slow-progressing condition that usually becomes symptomatic in the fifth and sixth decades of life. As the U.S. population ages, the prevalence of this disease is expected to increase (2). Chronic obstructive

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Table 1. Available Staging Systems for Chronic Obstructive Pulmonary Disease*

Staging System	Mild	Moderate	Severe
Stable COPD			
European Respiratory Society guidelines (7) FEV ₁	≥70%	50% to 69%	<50%
American Thoracic Society guidelines (8)† FEV ₁	≥50%	35% to 49%	<35%
British Thoracic Society guidelines (9) FEV ₁	60%–79% predicted	40%–59% predicted	<40% predicted
Cough	“Smoker’s cough”	Cough with or without sputum	Prominent cough
Dyspnea	Minimal	On exertion	On exertion or at rest
Findings on lung examination	Normal	With or without wheeze	Hyperinflation, wheeze
Findings on other examinations	Normal	Normal	Cyanosis, edema
Acute exacerbations of COPD			
3 cardinal symptoms (worsening of dyspnea, increase in sputum purulence, increase in sputum volume) outlined by Anthonisen et al. (6)‡	1 of 3 cardinal symptoms as well as 1 of the following: upper respiratory tract infection in past 5 days, fever without other apparent cause, increased wheezing, increased cough, increase in respiratory rate or heart rate by 20% above baseline	2 of 3 cardinal symptoms	All 3 cardinal symptoms

* COPD = chronic obstructive pulmonary disease. Numbers in parentheses are reference numbers.

† Mild = type 1; moderate = type 2; severe = type 3.

‡ Mild = type 3; moderate = type 2; severe = type 1.

pulmonary disease currently accounts for approximately 110 000 deaths per year, making it, after heart disease, cancer, and stroke, the fourth leading cause of death. Nonasthma COPD in the United States annually accounts for 16 367 000 office visits, 500 000 hospitalizations, and \$18 billion in direct health care costs (3, 4).

The term *COPD* is used to describe a range of pathophysiologic entities characterized by airflow obstruction, including chronic bronchitis, emphysema, asthma, and bronchiectasis. In this paper and the accompanying guideline, we focus on the care of patients with the first two diagnoses. This approach is consistent with the National Heart, Lung, and Blood Institute’s definition of COPD as an “umbrella term used to encompass several more specific respiratory conditions,” including chronic (obstructive) bronchitis and emphysema (5). In fact, separating these entities is difficult both when evaluating clinical studies and when practicing clinical medicine.

Causes of COPD include smoking (85% to 90% of all cases), genetic factors (including α_1 antitrypsin deficiency), passive smoking, occupational exposures, air pollution, and possibly hyperresponsive airways. Although precise distinctions between chronic bronchitis and emphysema are a subject of debate, tradition holds that chronic bronchitis is responsible for 85% of COPD. Patients with chronic bronchitis experience in-

termittent airway inflammation that leads to frequent, prolonged episodes of productive cough. In contrast, 15% of patients with COPD primarily have emphysema, a disease in which the infrastructure of alveoli and distal airspaces, and therefore the portion of the lung that provides elastic recoil, is destroyed. Both conditions predispose patients to a common constellation of symptoms and signs and a collection of impairments in respiratory function.

Spirometric testing is used to confirm the diagnosis of COPD. Typical abnormalities include a decrease in FEV₁ and a decrease in the ratio of FEV₁ to FVC. Other abnormalities include an increased residual volume and total lung capacity and a limited and incomplete response of FEV₁ to bronchodilators (incomplete reversibility). Diffusing capacity for carbon monoxide is often diminished in emphysema, and response to bronchodilators can be seen in patients with concomitant asthma. Several staging systems are available for patients with stable COPD. The staging systems of both the European Respiratory Society and the American Thoracic Society use FEV₁ as the sole staging characteristic because it is most closely correlated with mortality and frequency of acute exacerbation. The British Thoracic Society staging system also includes clinical features of a patient’s cough, sputum, dyspnea, and lung sounds (Table 1).

In evaluating the published literature and in developing practice guidelines, we have attempted to adhere to a generally accepted and useful concept of an “acute exacerbation” or “flare” of COPD. However, many definitions exist, many authors use substantively different criteria, and many studies describe their inclusion criteria poorly. In general, most published definitions involve some combination of three clinical findings: worsening of dyspnea, increase in sputum purulence, and increase in sputum volume. Unlike the staging systems for stable COPD, there are no standardized, validated grading systems for severity of an acute exacerbation. Probably the most commonly used system is that developed by Anthonisen and colleagues (6). In this system, patients with type 1 (severe) exacerbations have all three of the main clinical findings and those with type 2 (moderate) exacerbations have two of the three. Patients with type 3 (mild) exacerbations have at least one of these clinical findings and at least one of the following clinical criteria: an upper respiratory infection in the past 5 days, fever without other apparent cause, increased wheezing, increased cough, or increase in respiratory rate or heart rate by 20% above baseline (Table 1). Clinicians should be aware that other conditions, such as heart failure and pulmonary embolism, can mimic an acute exacerbation.

Tracheobronchial infections are believed to be a common inciting cause of acute exacerbations of COPD. However, controversy surrounds the nature of the infectious agent as well as its exact role. Sputum obtained from patients with mild to moderately severe chronic bronchitis routinely culture a variety of bacteria, including *Haemophilus influenzae* (22%), *Pseudomonas aeruginosa* (15%), *Streptococcus pneumoniae* (10%), and *Moraxella catarrhalis* (9%) (10). Nonpathogenic bacteria, such as *H. parainfluenzae*, account for up to one third of all isolates. Also, certain groups of patients, such as those living in nursing homes, those recently treated with antibiotics, and those admitted to intensive care units, are more likely to be colonized with resistant organisms, such as *Pseudomonas* species. The role of these colonizers in the pathogenesis of acute exacerbation remains unclear, and their presence makes interpretation of any sputum culture difficult. Some investigators have also proposed that *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* may precipitate between 1% to 10% of exacerbations (11–13). Others have pointed out that

the presence of eosinophilic inflammation in bronchial biopsy specimens from patients with exacerbations may indicate that viruses (notably rhinovirus) play an important role (14, 15).

Acute exacerbations are clearly associated with environmental exposures as well. Significant correlations between levels of respirable particles (diameter < 10 μm) and ozone have been linked to hospital admission rates (16). Finally, severe exacerbations may be precipitated by other serious clinical conditions, such as heart failure, nonpulmonary infections, pulmonary embolism, and pneumothorax (17).

The outcomes of COPD exacerbations are similarly heterogeneous. Although nearly 50% of exacerbations are not reported to physicians (18, 19), exacerbations requiring hospitalization are associated with an inpatient mortality rate of 3% to 4% (20). Mortality rates are substantially higher among patients who require treatment in an intensive care unit (11% to 24% in-hospital and 43% to 46% by 1 year) (17, 21–24). After an acute exacerbation, most patients are expected to experience at least a temporary decrease in functional status and quality of life (19, 25, 26), and 50% of those hospitalized for the condition are expected to be readmitted at least once in the ensuing 6 months (17, 27).

1.0 METHODS

Identification of Topics for Literature Search

Topics to be covered in this paper and in the practice guideline were determined through a consensus process that involved both the ACP–ASIM/ACCP expert panel and the technical advisory panel of the Evidence-Based Practice Center at Duke University. The topic list was generated to address three questions: 1) What information is available to aid clinicians in predicting the clinical course of a patient with an acute exacerbation? 2) What information is available about the utility of diagnostic tests used to evaluate patients with symptoms of acute exacerbation? 3) What information is available to help guide clinicians in using available therapies and interventions? We did not consider care of patients with chronic, stable COPD; experimental therapies that are not widely available; or invasive mechanical ventilation.

Search Strategy

We gathered information through systematic searches and ongoing surveillance of MEDLINE (1966 to 2000,

Table 2. External Validity Scale*

Validity of the underlying COPD diagnosis
COPD diagnosis based on spirometry†
Yes = 1
No = 0
Baseline stable ventilatory status (for example, FEV ₁) of study sample described
Yes = 1
No = 0
Validity of diagnosis of acute exacerbation of COPD
Definition of acute exacerbation of COPD includes at least two of the following:
Increased sputum purulence
Increased sputum volume
Increased dyspnea
Yes = 1
No = 0
Characterization of severity of acute exacerbation of COPD
Study describes the severity of acute exacerbation of COPD at enrollment based on at least two of the following:
Mental status change
Work of breathing (that is, respiratory rate or use of accessory muscles)
Ventilatory status (that is, FEV ₁ or peak expiratory flow rate; PCO ₂ and either O ₂ saturation or PO ₂)
Yes = 1
No = 0
Duration of follow-up (treatment articles only)
Outcomes assessed at 24 hours or later
Yes = 1
No = 0

* Studies were assigned ratings on the basis of the number of criteria validated. COPD = chronic obstructive pulmonary disease.

† Based on reference 7.

week 5), EMBASE (1974 to 2000, week 18), HealthStar (1975 to June 2000), and the Cochrane Controlled Trials Register (2000, Issue 1). Search strategies included the index terms and textwords *chronic obstructive pulmonary disease* and *acute exacerbation* and specific terms relating to interventions and outcomes. Variations on several search strategies were tested in order to locate the greatest number of relevant articles. The abstracts of relevant articles were reviewed against predetermined criteria and appropriate articles were retrieved; reference lists of retrieved articles were also examined. We obtained 707 full-text articles through this process. Those that were eligible for analysis were summarized in evidence tables, and the data, study methods, and evidence available in each article were evaluated.

Assessment of the Quality of Available Evidence

Each retrieved study was evaluated along two dimensions: 1) To what extent did the study enroll the patients in whom we were interested (external validity)? 2) To what extent did the study follow the optimal design (internal validity)? Our criteria for external valid-

ity hinged on two questions: 1) Did the study enroll patients who had COPD according to a conventional definition (Table 1)? 2) Did the study enroll patients with acute exacerbations of COPD as documented by a description of both the cohort's symptoms and the diagnostic testing that was used to exclude other causes? On the basis of the adequacy of each study's documentation of these two concerns, we generated a scoring system for external validity (Table 2) that ranged from 0 (poorest quality) to 5 (highest quality). Sample size was not considered, and all comments about the significance of the results reflect that the authors reported statistical significance with a *P* value less than 0.05.

We used different criteria for internal validity when evaluating experimental and observational studies. To evaluate experimental studies, we used the scoring system described by Jadad and coworkers (28), which assigns scores based on the quality of design of randomized, controlled trials (Table 3). Specifically, scores range from 0 to 5 and points are earned for adequate randomization, blinding, and assessment of withdrawals and dropouts. To evaluate observational studies, we used the hierarchy of evidence proposed by the Center for Evidence-Based Medicine (29) (Table 4). Unlike the Jadad scale for experimental designs, lower scores for internal validity of observational studies denote a higher level of evidence. For studies that presented prognostic models, clinical prediction rules, or severity-of-illness algorithms, we assessed the extent of model validation

Table 3. Internal Validity Scale for Experimental Studies*

Was the study described as randomized?
Yes = 1
No = 0
Was the method of randomization well described and adequate?
Not described = 0
Described and adequate = 1
Described but not adequate = -1
Was the study described as double-blind?
Yes = 1
No = 0
Was the method of double-blinding well described and adequate?
Not described = 0
Described and adequate = 1
Described but not adequate = -1
Was the description of withdrawals and dropouts sufficient to determine the number of patients in each treatment group entering and completing the trial?
Yes = 1
No = 0

* Based on reference 28.

Table 4. Internal Validity Scale for Observational Studies*

Grade of Recommendation	Level of Evidence	Prognosis	Diagnosis
A	1a	Systematic review (with homogeneity) of inception cohort studies or a clinical practice guideline validated on a test set	Systematic review (with homogeneity) of level 1 diagnostic studies or a clinical practice guideline validated on a test set
	1b†	Individual inception cohort study with ≥80% follow-up	Independent blinded comparison of an appropriate spectrum of consecutive patients, all of whom have undergone both the diagnostic test and the reference standard
	1c	All-or-none case series	Absolute SpPins and SnNouts‡
	2a	Systematic review (with homogeneity) of either retrospective cohort studies or untreated control groups in randomized, controlled trials	Systematic review (with homogeneity) of studies with an internal validity score ≥ 2
	2b§	Retrospective cohort study or follow-up of untreated control patients in a randomized, controlled trial, or clinical practice guideline not validated in a test set	Independent blinded comparison in nonconsecutive patients or confined to a narrow spectrum of study patients (or both), all of whom have undergone both the diagnostic test and the reference standard, or a diagnostic clinical practice guideline not validated in a test set
B	2c	“Outcomes” research	Independent blinded comparison of an appropriate spectrum in which the reference standard was not applied to all study patients
	3		
C	4	Case series (and poor-quality prognostic cohort studies)	Reference standard was not applied independently or was not applied blindly
D	5	Expert opinion without explicit critical appraisal, or expert opinion based on physiology, bench research, or “first principles”	Expert opinion without explicit critical appraisal, or expert opinion based on physiology, bench research, or “first principles”

* Reproduced with permission from reference 29. *Homogeneity* means free of worrisome variations in the directions and degrees of results between individual studies.
 † Well-designed prospective studies were included in this category.
 ‡ An “Absolute SpPin” is a diagnostic finding whose *specificity* is so high that a *positive* result rules *in* the diagnosis; an “absolute SnNout” is a diagnostic finding whose *sensitivity* is so high that a *negative* result rules *out* the diagnosis.
 § Includes inception cohort studies with <80% follow-up and retrospective studies.
 || Includes studies in which sampling was biased in favor of patients who already had the target outcome; the measurement of outcomes was accomplished in <80% of study patients; outcomes were determined in an unblinded, nonobjective way; or findings were not corrected for confounding.

reported by using the system proposed by Justice and colleagues (30) (Table 5). This scoring system ranges from 0 to 5; higher scores show that the prediction model was more extensively evaluated on independent patient samples.

Scores for studies that appear in the tables are given in the tables, and scores for studies that appear only in the text are given in the text. External validity is documented as a ratio of the total number of points earned divided by the number of points possible (for example, 3 of 5 points) (Table 2). For internal validity, it was nec-

essary to consider the type of study (experimental or observational). Experimental studies received a score based on the scale described in Table 3, while the level of evidence in observational studies was evaluated on the basis of the scale described in Table 4. The degree of validation of prognostic models is relevant only to the studies presented in Tables 6 and 7.

Choice of Inclusion of Studies for Reporting and Analysis

The minimum threshold for inclusion of different study designs was driven by the relative availability of studies in each category. Randomized, placebo-controlled studies are considered to produce the highest level of evidence, but information from these types of studies was scanty or lacking for some treatment and diagnostic methods. We chose a different threshold of inclusion for each topic on the basis of the availability of relevant data (Table 8). The varying quality of the assessed studies is taken into account in the evaluation.

Table 5. Degree of Validation of Predictive Models

Level of Validation	Description
0	Internal validation
1	Prospective validation
2	Independent validation
3	Multisite validation
4	Multiple independent validations
5	Multiple independent validations with life-table analyses

Table 6. Predictors of Relapse Analyzed in More Than One Study*

Variable	Study (Reference)									
	Fedullo et al. (31)	Murata et al. (32)	Emerman et al. (33)	Murata et al. (34)	Murata et al. (35)†	Murata et al. (36)†	Ball et al. (37)	Parshall (38)	Adams et al. (39)	Dewan et al. (40)
Study year	1986	1989	1991	1991	1992a	1992b	1995	1999	2000	2000
Internal validity score/external validity score‡	2b/1	2b/2	1b/2	2b/4	2b/2	2b/2	1b/1	1b/0	4/3	2b/2
Degree of validation of predictive model	0	0	0	0	2	0	0	0	0	0
Patients, <i>n</i>	24	268	83	352	289	213	471	239	173§	107
Predictors										
Patient demographic characteristics										
Older age	–		+		–	–	–	–	–	–
Female sex			+				–		–	
Smoking history			–				–		–	
Clinical characteristics										
Increased body temperature	+			–	–					
Increased heart rate	–			–	–					
Increased respiratory rate	–			–	–					
Increased leukocyte count	–		–	–						
Hypertension									–	–
Diabetes									–	–
Liver disease									–	–
Chronic renal failure									–	–
Heart disease/heart failure							+		+	–
Pulmonary function tests										
Percentage recovery of FEV ₁				–		–				
Increased Pao ₂	+		–	–						
Decreased Pao ₂	+		–	–						
Decreased pH	+		–	–						
Decreased post-treatment FEV ₁			–	+		+				
Decreased pretreatment FEV ₁			+	+		–				+
Severity of exacerbation							–		–	
Abnormal findings on auscultation	–						–			
Emergency department timing and visits										
Increase in admission rate of previous visits					–	+				
Previous visit within 7 days					+	–				
Increase in relapse rate of previous visits					+	+				
Nighttime admission		+			–	–				
Treatment										
Use of home oxygen					–				+	+
Weekend visit		+				–				
Shorter duration of dyspnea				+				+		
Aminophylline treatment			–	–	+					
No antibiotics on discharge				–	–				+	
Length of treatment		–	–	–	–					
Increased number of bronchodilator treatments			+	+	+			–	–	
Oral prednisone at entry				–	–					
No oral prednisone at discharge				+	+					
Steroid treatment in emergency department			–	–	–				–	

* Plus sign indicates statistically significant association with relapse; minus sign indicates no statistically significant association with relapse.

† These studies contain partially overlapping study samples.

‡ Indicates score out of a possible total of 4 points.

§ 362 patient visits were analyzed from a sample of 173 patients.

|| 232 exacerbations were analyzed from a sample of 107 patients.

Table 7. Statistically Significant Predictors of Inpatient Mortality*

Study (Reference)	Year	Setting	Analysis	Patients, <i>n</i>	Validity			Significant Predictors of Mortality
					External Validity Score	Internal Validity Score	Degree of Validation	
Connors et al. (17)	1996	ICU	Multivariable	1016	1	1b	3	Increased acute physiology score Decreased BMI Older age Decreased activities of daily living score Decreased PaO ₂ -FiO ₂ ratio Absence of comorbid chronic heart failure Decreased serum albumin level Absence of comorbid cor pulmonale
Seneff et al. (23)	1995	ICU	Multivariable	362	1	1b	0	Increased nonrespiratory acute physiology score Increased number of pre-ICU hospital days
Burk and George (21)	1973	Hospital ward/ICU	Univariable	74	1	2b	0	Use of mechanical ventilation (vs. conservative care) General medical ward care (vs. ICU care) Chronic heart failure as cause of acute respiratory failure (vs. respiratory infection)
Warren et al. (41)	1980	Hospital ward	Univariable	135	2	2b	0	Older age Highest level of arterial PaCO ₂ during controlled oxygen therapy
Jeffrey et al. (42)	1992	Hospital	Univariable	95	2	1b	2	Lowest pH < 7.26 (<i>P</i> < 0.025) Measured at admission Increased blood urea concentration Decreased systolic blood pressure Decreased arterial pH Measured throughout hospital stay Lowest pH < 7.26 Lowest pH < 7.28
Heuser et al. (43)	1992	ICU	Multivariable	3050	0	2b	0	Older age Primary diagnosis pneumonia (vs. asthmatic bronchitis)
Portier et al. (22)	1992	ICU	Multivariable	322	1	1b	0	MedisGroups admitting severity group 3 or 4 Presence of cachexia Decreased serum sodium level Required mechanical ventilation in first 24 h COPD not underlying chronic respiratory insufficiency Previous confinement to home
Fuso et al. (44)	1995	Hospital	Multivariable	590	3	2b	0	Presence of edema Older age PAO ₂ - PaO ₂ > 41 mm Hg Presence of atrial fibrillation Presence of ventricular arrhythmias

* BMI = body mass index; COPD = chronic obstructive pulmonary disease; FiO₂ = fraction of inspired oxygen; ICU = intensive care unit; PAO₂-PaO₂ = alveolar-arterial difference in partial pressure of oxygen.

2.0 APPROACH TO THE PATIENT WITH AN ACUTE EXACERBATION OF COPD

In the following section, we discuss our recommendations and findings regarding three domains of care for patients with acute exacerbations of COPD: risk stratification of patients (specifically data on predictors of outpatient relapse and inpatient mortality); choice of diagnostic tests; and benefits and risks of therapeutic interventions, including mucus clearance strategies, bronchodilating agents, corticosteroids, antibiotics, oxygen,

and noninvasive mechanical ventilation. Three methodologic problems hindered our analysis. First, the care of patients with acute exacerbations of COPD is sometimes characterized as “shotgun therapy”—that is, most patients receive most available therapies. Therefore, many studies designed to evaluate one intervention include patients receiving other interventions. These co-interventions make analysis of the effects of single therapies more difficult, especially when co-interventions are not standardized. Second, many studies evaluate changes

in FEV₁ as the primary outcome of interest because it can be safely and easily measured. This measure of respiratory function, although a reliable predictor of other clinical outcomes, is relatively insensitive to changes in clinical condition when compared with other quantitative measures (such as arterial blood gas values) and with qualitative evaluations of symptoms (18, 45). Finally, although most studies addressed care of patients in emergency departments or inpatient settings, many patients with milder acute exacerbations do not receive care in these settings. Therefore, our conclusions are more focused on care of patients with more severe exacerbations.

2.1 Risk Stratification

2.1.1 Prediction of Outpatient Relapse

On the basis of 10 studies that evaluated patients with acute exacerbations of COPD in emergency departments (7 studies) and in the outpatient setting (3 studies), we conclude that certain characteristics are associated with a need for additional treatment rather than gradual improvement (Table 6). The ability to identify patients at high risk for relapse should improve decisions about hospital admission and follow-up appointments. Several investigators have confirmed that relapse is more likely among patients who have lower pretreatment or post-treatment FEV₁, those who receive more bronchodilator treatments or corticosteroids during their visit, and those who have higher rates of previous relapse. At present, available prediction models can provide clinical guidance on the basis of these identified predictors. It should be noted that these models, however, have only moderately good discriminatory power. For example, the best model for predicting relapse (defined as return to the emergency department < 14 days after initial presentation) had a sensitivity of 57% and a specificity of 72% (35).

2.1.2 Prediction of Inpatient Mortality

On the basis of 11 studies, we conclude that certain physiologic characteristics are associated with a higher likelihood of inpatient death. Prediction models that include these characteristics are potentially useful for risk stratification in population-based and randomized studies. However, when these characteristics are used to influence decisions about instituting, continuing, or withdrawing life-sustaining therapies, caution should be

Table 8. Inclusion Thresholds by Topic

Topic	Weakest Study Design Included
Diagnosis or prognosis	Cohort design
Mucus clearance strategies	Randomized, placebo-controlled trial
Bronchodilating agents	Randomized, agent-to-agent comparisons
Corticosteroids	Randomized, placebo-controlled trial
Antibiotics	Randomized, placebo-controlled trial
Oxygen therapy	Observational cohort
Noninvasive positive-pressure ventilation	Randomized, controlled trial; observational cohort

exercised. We identified no prediction models that were able to identify patients who were almost certain to die ($\geq 90\%$ likelihood of death) during their inpatient stay. It should also be noted that inclusion criteria varies greatly in these studies, raising concerns about the external validity of some of these results. Of the 11 studies, 8 (Table 7) documented an association between specific clinical predictors and mortality, while the other 3 did not report significant predictors (20, 46, 47). We summarize the two largest studies examining this outcome.

The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) enrolled 1016 patients who had acute exacerbations of COPD at hospital admission (17). The exacerbations had various causes, including respiratory infection (including pneumonia) (48%), congestive heart failure (26%), lung cancer (3.3%), pulmonary embolus (1.4%), and pneumothorax (1%). The outcome of interest, 180-day mortality rate, was 33% (the 2-year mortality rate was 49%). Significant predictors were worse Acute Physiology and Chronic Health Evaluation (APACHE) III score (48), lower body mass index, older age, worse functional status 2 weeks before admission, lower ratio of PO₂ to fraction of inspired oxygen, history of congestive heart failure, lower serum albumin level, presence of cor pulmonale, lower activities of daily living scores, and lower score on the Duke Activity Status index. Predictions from the model that included these variables showed good calibration (calibration index, 0.0016) and fair discrimination (area under the receiver-operating characteristic curve, 0.731) in a validation cohort.

Another large prospective cohort study enrolled 362 patients who were admitted to intensive care units with COPD-related respiratory failure. Patients with pneumonia, pulmonary edema, or pulmonary embolus were excluded. The in-hospital mortality rate, 23.8%, was

Table 9. Randomized Trials of Corticosteroid Agents

Study (Reference)	Year	Sample Size, <i>n</i>	Corticosteroid Agent	Equivalent First-Day Dose of Methylprednisolone, <i>mg</i>	End Point
Bullard et al. (78)	1996	138	Hydrocortisone (100 mg intravenously once)	20	Increased FEV ₁ from 0 to 6 hours
Davies et al. (79)	1999	56	Prednisolone (orally, 30 mg/d for 14 d)	37.5	Increased mean percentage predicted prebronchodilator FEV ₁ Increased mean percentage predicted postbronchodilator FEV ₁
Thompson et al. (80)	1996	27	Prednisone (orally, 60 mg/d for 3 d, then tapered)	75	Decreased length of stay Increased mean slope of FEV ₁ Percentage change in FEV ₁ from day 1 to day 10
Emerman et al. (81)	1989b	100	Methylprednisolone (100 mg intravenously once)	100	Decreased length of stay Increased FEV ₁ (percentage improvement) Hospital admission rate
Albert et al. (82)	1980	44	Methylprednisolone (35 mg [based on 0.5 mg/kg body weight] intravenously every 6 h for 3 d)	140	Increased FEV ₁ (percentage change prebronchodilator) Increased FEV ₁ (percentage change postbronchodilator)
Niewoehner et al. (83)	1999	271	Methylprednisolone (125 mg intravenously every 6 h for 3 d, followed by oral prednisone taper)	500	Decreased length of stay Increased FEV ₁ at days 1, 2, and 3

* Plus sign indicates beneficial effect of corticosteroid over placebo; minus sign indicates beneficial effect of placebo over corticosteroid.

† Plus sign indicates beneficial effect of corticosteroid over course of treatment.

‡ Statistically significant effect.

§ *P* value not reported.

predicted by the number of hospital days before transfer to the intensive care unit and the nonrespiratory component of the APACHE III score. A separate analysis identified three predictors of 180-day mortality: acute physiology score, old age, and more hospital days before transfer to the intensive care unit. Activities of daily living were also a significant predictor on univariable analysis (23).

2.2 Diagnostic Testing

2.2.1 General Approach

Many assessment techniques are frequently used to evaluate patients with acute exacerbations of COPD. These include measuring routine laboratory values, performing a physical examination, performing electrocardiography, assessing cardiac function, and instituting an empirical trial of diuretics. We found no published evidence that could help us determine the utility of these approaches. For another commonly used assessment, arterial blood gas sampling, we found indirect evidence in many studies to support its clinical utility. These studies, which are covered in detail in other parts of this report, demonstrate that arterial blood gas analysis is

helpful both in terms of gauging the severity of an exacerbation and in identifying patients currently in need of oxygen therapy and those potentially in need of mechanical ventilatory support. We also examined evidence on two other diagnostic methods, chest radiography and spirometric testing.

2.2.2 Chest Radiography for Establishing Causes and Coexisting Illnesses

On the basis of three observational studies, we conclude that for patients treated in emergency departments or hospitals, chest radiography is a useful diagnostic test. A substantial rate of abnormalities on chest radiography was documented in two retrospective studies. One study evaluated 685 visits at which chest radiography was performed in a single urban emergency department and found a 16% abnormality rate (49) (external validity, 0 of 4 points; internal validity, 2b). The second study found a 16% abnormality rate (7% judged as “clinically significant”) in 107 patients admitted to a single hospital (50) (external validity, 0 of 4 points; internal validity, 2b). In a prospective cohort study of 128 hospital admissions for asthma or COPD, 21% of patients had a

Table 9—Continued

Steroid Compared with Placebo*	Steroid over Time†	Validity Score
	+‡	External: 1/5; internal: 4/5
+	+‡	External: 4/5; internal: 5/5
+	+‡	
+‡		
+‡		External: 5/5; internal: 3/5
+‡		
–		External: 3/5; internal: 4/5
–	+§	
–		
+‡		External: 4/5; internal: 5/5
+‡		
+‡		External: 2/5; internal: 4/5
+‡		

change in management that was prompted by results on chest radiography; most had new pulmonary infiltrates or evidence of congestive heart failure (51) (external validity, 1 of 4 points; internal validity, 1b). Models presented by these authors for predicting abnormalities on chest radiography were not reliable enough to be clinically useful.

2.2.3 Spirometric Testing

Several studies have shown that FEV₁ is loosely correlated with relapse rate. However, on the basis of three observational studies, we conclude that spirometric assessment at presentation or during treatment is of limited usefulness in the care of patients with acute exacerbations of COPD. In this disease, changes in clinical status are not usually well correlated with changes in spirometric measures. A study performed in 70 patients in an urban emergency department demonstrated that FEV₁ at presentation was weakly but statistically significantly correlated with both PCO₂ ($r = -0.46$; $P < 0.001$) and pH ($r = 0.33$; $P < 0.01$) but was not correlated with arterial PO₂ (external validity, 3 of 4 points; internal validity, 1b) (52). These results are different

from those seen in studies of patients with asthma who present to the emergency department; these studies showed high correlation between spirometry and arterial blood gas values. Another study of 199 patients presenting with acute exacerbation of COPD in an urban emergency department demonstrated that peak expiratory flow rate and FEV₁ are correlated ($r = 0.84$; $P < 0.001$) (53). The clinical implication of this finding, however, is unclear (external validity, 1 of 4 points; internal validity, 1b). Furthermore, in this study, a substantial minority of patients had absolute discrepancies between percentage predicted FEV₁ and percentage predicted peak expiratory flow rate exceeding 10 points.

2.3 Therapeutic Interventions

2.3.1 Bronchodilating Agents

On the basis of 14 randomized studies, we make the following conclusions: 1) Short-acting β -agonist-type and anticholinergic-type inhaled bronchodilators have similar effects on spirometry and a greater effect than all parenterally administered bronchodilators (that is, parenteral methylxanthines and sympathomimetics); 2) the toxicity profile of the methylxanthine agents makes them potentially harmful; and 3) some patients may experience additional benefit when a second bronchodilating agent is administered after the maximal dose of the initial inhaled bronchodilator is reached. These generalizations are limited by the small number of analyzable trials published, substantial differences in inclusion and exclusion criteria, and the varied drug dosages that were studied (54, 55).

Five randomized, controlled trials compared individual bronchodilating agents. Two compared the efficacy of inhaled ipratropium bromide with that of short-acting β -agonists. The first study (55) enrolled 40 patients and observed that among those receiving ipratropium, FEV₁ showed statistically significant improvement from day 1 to day 7 at 15 and 30 minutes after administration. However, no significant differences were seen at 0, 5, 10, 60, 120, and 240 minutes after administration. Similarly, the only significant improvement observed in patients receiving fenoterol was at 60 minutes after treatment on day 7 ($P < 0.05$) (external validity, 2 of 5 points; internal validity, 3 of 5 points). The second study (56) involved 32 patients in a crossover design comparing ipratropium and metaproterenol. At

Table 10. Characteristics of Randomized, Controlled Trials of Antibiotics in Acute Exacerbations of Chronic Obstructive Pulmonary Disease*

Study (Reference)	Year	Patients <i>n</i>	Medication in Treatment Group	Medication in Control Group	Mean PEFR at Entry	Patients with Purulent Sputum	Level of Care	Glucocorticoid Use
					<i>L/min</i>	%		
Jørgensen et al. (87)	1992	268	Amoxicillin	Placebo	295†	33§	Outpatient	Prohibited
Sachs et al. (93)	1995	71	Amoxicillin or TMP-SMX	Placebo	233	27	Outpatient	Prescribed
Petersen et al. (89)	1967	19	Chloramphenicol	Placebo	214	74	Inpatient	NS
Anthonisen et al. (6)	1987	173	TMP-SMX, amoxicillin, or doxycycline	Placebo	190	60	Outpatient	Permitted (42% of all patients)
Nicotra et al. (88)	1982	40	Tetracycline	Placebo	160	NS	Inpatient	Permitted (75% of antibiotic group; 65% of placebo group)
Pines et al. (90)	1972	259	Tetracycline or chloramphenicol	Placebo	146	100**	Inpatient	NS
Pines et al. (92)	1968	30	Penicillin and streptomycin, penicillin alone	Placebo	88	100	Inpatient	NS
Elmes et al. (91)	1965	58	Ampicillin	Placebo	79	78	Inpatient	Prohibited
Berry et al. (84)	1960	53	Oxytetracycline	Placebo	NS	60	Outpatient	NS
Elmes et al. (85)	1957	59	Oxytetracycline	Placebo or no treatment	NS	NS	Outpatient	NS
Fear and Edwards (86)	1962	62	Oxytetracycline	Placebo	NS	NS	Outpatient	NS

* NS = not specified; PEFR = peak expiratory flow rate; TMP-SMX = trimethoprim-sulfamethoxazole.
 † Plus sign indicates benefit of antibiotic recipients over placebo recipients; equal sign indicates no reported benefit of antibiotic recipients over placebo recipients.
 ‡ Estimated from the Figure.
 § Sputum color: yellow vs. none, clear, or white.
 || Weighted average of men's median PEFR and women's median PEFR in the control group (*n* = 10); value for active treatment group could not be similarly estimated.
 ¶ *P* < 0.05.
 ** Moderately purulent or purulent.

30 minutes after administration, patients receiving ipratropium had a significant increase in PaO₂, while those receiving metaproterenol had a significant decrease in PaO₂. At 90 minutes, these differences had disappeared, and both patient groups showed a significant improvement in FEV₁. However, no additional improvement was seen after the patients crossed over to treatment with the second drug (external validity, 3 of 5 points; internal validity, 5 of 5 points). In a study of 90 patients with asthma, COPD, or both who were being transported to an emergency department (57), nebulized albuterol was compared with subcutaneous terbutaline. Patient-perceived improvement, respiratory rate, and dyspnea rating improved significantly only in the group receiving albuterol (*P* < 0.05) (external validity, 0 of 5 points; internal validity, 5 of 5 points). In a dosing study involving 86 patients (58), FEV₁ did not differ signifi-

cantly at 2 hours in patients who received nebulized albuterol, 2.5 mg, every 20 minutes and those who received it every hour. However, the findings suggested that patients with lower FEV₁ may have benefited from the first regimen (external validity, 1 of 5 points; internal validity, 4 of 5 points).

The addition of a methylxanthine to inhaled bronchodilators was examined in three randomized studies. One study (59), which involved 143 patients with asthma and COPD receiving care in an emergency department, reported a trend toward lower hospitalization rates for patients treated with aminophylline in addition to short-acting β-agonists and corticosteroids (external validity, 1 of 5 points; internal validity, 3 of 5 points). Two studies (60, 61) found no significant difference in measured changes in FEV₁ between patients receiving standard therapy (including short-acting β-agonists) and

Table 10—Continued

Result†	Validity Score
Overall clinical assessment =; physician-assessed symptoms, = PEFR, =	External: 2/5; internal: 3/5
Patient-assessed symptoms, + PEFR, +	External: 4/5; internal: 4/5
PEFR, =	External: 2/5; internal: 5/5
Overall clinical assessment, +¶; PEFR, +¶	External: 5/5; internal: 4/5
Patient-assessed symptoms, = Physician-assessed symptoms, =	External: 4/5; internal: 4/5
FEV ₁ , PEFR, FVC, =	
Overall clinical assessment, +¶ Physician-assessed symptoms, +¶ PEFR, +	External: 3/5; internal: 4/5
Overall clinical assessment, +¶	External: 2/5; internal: 5/5
Overall clinical assessment, = PEFR, + Length of stay, =	External: 2/5; internal: 5/5
Physician-assessed symptoms, patients with moderate to severe exacerbations, +¶	External: 2/5; internal: 3/5
Duration of symptoms, + Work days lost, +	External: 2/5; internal: 5/5
Physician-assessed symptoms, +; duration of symptoms, +	External: 2/5; internal: 5/5

those who also received aminophylline (external validity, 4 of 5 points and 1 of 5 points, respectively; internal validity, 5 of 5 points and 4 of 5 points, respectively).

Seven randomized studies have examined the effect of adding a second class of bronchodilator (for example, anticholinergic agent or short-acting β -agonist) to a full-dose regimen of the other agent. Six of these studies specifically examined the impact of an anticholinergic agent added to a short-acting β -agonist for treatment of acute exacerbations of COPD. In a study of 57 patients in the emergency department (62), the FEV₁ increase was larger in patients who received glycopyrrolate and albuterol than in those who received albuterol alone (external validity, 2 of 5 points; internal validity, 4 of 5 points). A study of 68 patients in the emergency department (63) found that although length of stay was significantly shorter in patients who received ipratropium

and isoetharine than in those who received isoetharine alone, admission rates to the hospital were similar (external validity, 1 of 5 points; internal validity, 5 of 5 points). Three other studies (54, 64, 65) were unable to detect a difference in spirometry (FEV₁, FVC, or both) in patients treated with short-acting β -agonists alone when compared with those who were also given anticholinergic agents (external validity, 1 of 5 points, 3 of 5 points, and 1 of 5 points, respectively; internal validity, 2 of 5 points, 1 of 5 points, and 4 of 5 points, respectively). A three-armed study (66) examined 52 patients in the emergency department who received a short-acting β -agonist alone (fenoterol), an anticholinergic agent (ipratropium), or both agents. At 90 minutes, patients in all three groups experienced similar improvement in FEV₁. Patients receiving ipratropium alone had the lowest rate of reported side effects (external validity, 2 of 5 points; internal validity, 5 of 5 points).

Adverse effects of bronchodilators vary. The side effects of ipratropium bromide are generally fewer and milder. Three randomized, controlled trials (55, 63, 65) did not report any adverse effects with ipratropium bromide. Other effects include increased incidence of tremors and dry mouth (56, 66) and urinary retention when used in combination with albuterol (64). The adverse effects of albuterol include tremors, headache, nausea, vomiting, and palpitations. Adverse cardiovascular effects, such as changes in heart rate, blood pressure, and electrocardiography tracings, are also possible but rare (67). Adverse effects associated with theophylline include nausea, vomiting, headache, arrhythmias, and seizures (60, 68). The effects are more significant among patients with higher levels of theophylline.

On the basis of 8 randomized, controlled trials comparing metered-dose inhalers and nebulizers in patients with acute exacerbations of COPD, we conclude that there is insufficient evidence to determine that one method of delivery is superior to the other (69–76). Of the 8 studies, 6 described the use of spacer devices with metered-dose inhalers (69–71, 73, 75, 76), 1 specifically mentioned use of a metered-dose inhaler without a spacer (72), and 1 (an abstract) did not describe whether a spacer was used (74). The percentage improvement in FEV₁ was significantly greater after treatment with the nebulizer than with metered-dose inhalers in 2 studies (73, 74) but did not differ significantly in the other 6 studies. A meta-analysis of bronchodilator delivery

Table 11. Randomized Studies Comparing Noninvasive Positive-Pressure Ventilation with Nonventilatory Control*

Study (Reference)	Year	Patients		Intervention		Need for Intubation	
		NPPV Group	Control Group	Type	Duration	NPPV Group	Control Group
		<i>n</i>				<i>n/n (%)</i>	
Angus et al. (108)	1996	9	8	Nasal, pressure support	4 h once	NR	NR
Barbe et al. (109)	1996	10	10	Nasal, bilevel positive airway pressure	3 h twice per day	0 (0)	0 (0)
Bott et al. (110)	1993	30	30	Nasal, volume cycled	≤16 h/d	0/30 (0)	2/30 (7)
Brochard et al. (111)	1995	43	42	Face mask, pressure support	≥6 h/d	11/43 (26)‡	31/42 (74)
Kramer et al. (112)	1995	11	12	Nasal, bilevel positive airway pressure	≥8 h/d	1/11 (9)‡	8/12 (67)

* NPPV = noninvasive positive-pressure ventilation; NR = not reported.

† Blood gas improvement was defined differently in different studies. The results reported here are based on the definitions used in each study.

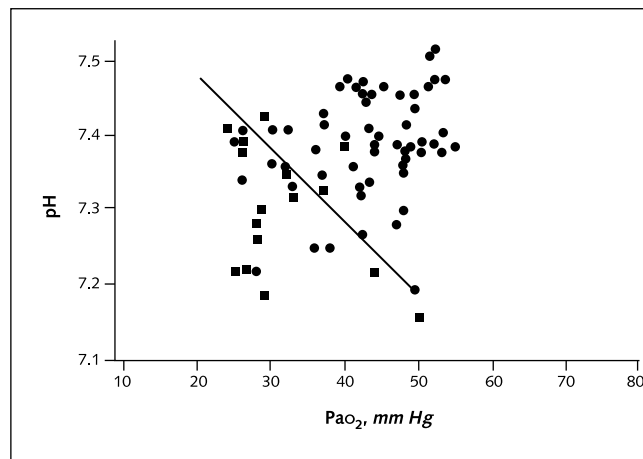
‡ Statistically significant within-group improvement ($P < 0.05$).

§ Statistical significance for within-group improvement was not reported.

devices in acute airflow obstruction included these studies of COPD and additional studies of patients with asthma (77). The meta-analysis found a negligible effect of nebulizers compared with metered-dose inhalers; this effect was not clinically or statistically significant. The doses of bronchodilator delivered by metered-dose in-

haler in these studies were lower than those delivered by nebulizer and those often used in clinical practice. Therefore, the few positive results may reflect differences in the dose of bronchodilator actually received. Furthermore, because all of the studies were small, they may have imprecisely estimated the efficacy of delivery by metered-dose inhalers compared with nebulizers.

Figure. Relationship among arterial pH, PaO₂, and risk for respiratory failure.



The discriminant function $pH = 7.66 - 0.00919 \times (PaO_2)$ helps identify patients at risk for CO₂ retention after the administration of supplemental oxygen. When the patient's observed PaO₂ is entered into the equation, the pH calculated can be compared with the measured pH to distinguish between high- and low-risk patients. If a patient is at high risk, the value calculated will be greater than that observed in the arterial blood gas. The symbols in the figure represent PaO₂ and pH values on admission of patients who were eventually intubated (squares) or not intubated (circles) in a study evaluating this predictive model. The diagonal line reflects values of the discriminant function and separates high- and low-risk patients. Adapted with permission from Bone et al. (98).

2.3.2 Corticosteroids

On the basis of six randomized, placebo-controlled studies, we conclude that a short course of systemic corticosteroids improves spirometry and decreases relapse rate in patients with acute exacerbation of COPD (Table 9). However, the optimal dose and duration of treatment remain uncertain, and few data document the efficacy of corticosteroids in outpatient settings. The evaluated studies varied greatly in dosage, length of treatment, administration, and setting (78–83). In the largest study, the Systemic Corticosteroids in Chronic Obstructive Pulmonary Disease Exacerbations (SCCOPE) trial, 271 patients admitted for an acute exacerbation of COPD at 1 of 25 Veterans Administration hospitals were assigned to receive placebo or 3 days of intravenous methylprednisolone followed by a course of oral prednisone (83). For the combined glucocorticoid group, the risk for treatment failure was reduced by 10 percentage points (33% vs. 23%), and FEV₁ improved by an average of approximately 0.1 L in the first 3 days of treatment. The change in FEV₁ is similar to the magnitude of benefit reported in smaller trials. The SCCOPE trial

Table 11—Continued

Mortality Rate		Blood Gas Improvement†			Validity Score
NPPV Group	Control Group	NPPV Group	Control Group	Statistically Significant between-Group Improvement	
<i>n/n (%)</i>					
0 (0) NR	3 (38) NR	Yes‡ Yes‡	No Yes‡	NR No	External: 3/5; internal: 1/5 External: 3/5; internal: 2/5
3/30 (10) 4/43 (9)‡	9/30 (30) 12/42 (29)	Yes§ Yes‡	No§ No	Yes NR	External: 2/5; internal: 2/5 External: 2/5; internal: 3/5
1/16 (6)	2/15 (13)	NR	NR	NR	External: 2/5; internal: 2/5

demonstrated equivalence between an 8-week regimen and a 2-week regimen, the latter of which consisted of methylprednisolone, 125 mg intravenously every 6 hours (days 1 to 3); oral prednisone, 60 mg/d (days 4 to 7); oral prednisone, 40 mg/d (days 8 to 11); and oral prednisone, 20 mg/d (days 12 to 15).

Several trials have examined the time course of improvement in FEV₁ during treatment with systemic corticosteroids. In the SCCOPE trial, the difference in FEV₁ between patients who received glucocorticoids and those who received placebo was highest after the first day of treatment, remained statistically significant after the second and third days, and was no longer significant at 2 weeks. Of the two trials that considered short-term outcomes of emergency department treatment, one observed similar improvements in FEV₁ between patients receiving corticosteroids and those receiving placebo (81). The other trial demonstrated a significant improvement in FEV₁ over time among patients receiving corticosteroids but did not compare them with those receiving placebo (78). Trials that measured changes in FEV₁ over longer periods, in contrast, have shown more conclusive results.

Hyperglycemia was the most common adverse effect associated with systemic corticosteroids for acute exacerbation of COPD (79, 83). In the SCCOPE trial, two thirds of hyperglycemic episodes requiring treatment occurred in patients who were known to have diabetes mellitus. Nearly all episodes occurred in the first 30

days. Whether hyperglycemia was more frequent or severe during the 8-week or 2-week course was not described (83).

2.3.3 Antibiotics

On the basis of 11 randomized, placebo-controlled studies of antibiotic treatment, we conclude that antibiotics are beneficial in the treatment of patients with acute exacerbations of COPD (6, 84–93) (Table 10). Patients with more severe exacerbations are more likely to experience benefit than those with less severe exacerbations. These conclusions are consistent with those of a recent meta-analysis that included many of the trials reviewed here (94). It should be noted that many of the studies that show benefit were performed before the emergence of respiratory pathogens that are resistant to multiple antibiotics.

In their 1996 meta-analysis, Saint and colleagues (94) included 9 randomized, controlled trials of antibiotics. These trials used a variety of outcome measures: peak expiratory flow rate, duration of exacerbation, PaO₂, symptom score, and overall severity score as determined by a physician. Three of 9 studies found a statistically significant benefit of antibiotics, 3 found a trend favoring antibiotics, and 3 failed to show any difference from placebo. The most consistently measured end point across studies, improvement in peak expiratory flow rate, was estimated to improve a mean of 10.75 L/min (95% CI, 4.96 to 16.54 L/min) more in

patients who received antibiotics than in those who received placebo.

Three of these studies analyzed the efficacy of antibiotics within subgroups defined either by evidence of bacterial infection or severity of illness (6, 84, 91). One trial found that a priori selection of patients with more severe exacerbations (using the previously mentioned grading system [Table 1]) identified those more likely to benefit from antibiotic treatment (6). Patients with type 1 (severe) exacerbations experienced benefit, and 63% of antibiotic-treated patients compared with 43% of placebo recipients improved. The benefit of antibiotic treatment was less apparent in patients with less severe exacerbations (70% vs. 60% for those with type 2 exacerbations and 74% vs. 70% for those with type 3 exacerbations). Another study demonstrated that physician-assigned severity was correlated with likelihood of benefit from antibiotics. Among patients with mild attacks, there were no significant differences between those who received antibiotics and those who received placebo. Among patients with moderate or severe attacks, patients treated with antibiotics had significantly less severe symptoms on days 2 and 7 (84). A third study demonstrated a similar relationship between severity of exacerbation and benefit from antibiotics. However, this study included patients with clinical evidence of pneumonia among those with severe exacerbations (91).

There is little evidence regarding the appropriate duration of administration of antibiotics. Typical administration periods range from 3 to 14 days in both placebo-controlled and head-to-head comparisons. A single retrospective study of patients receiving amoxicillin for acute exacerbations of COPD found a clinically favorable response in 70% of patients who received between 6 and 10 days of treatment. No follow-up assessment was performed (95).

2.3.4 Oxygen Therapy

Oxygen therapy provides enormous benefits to hypoxemic patients with acute exacerbations of COPD (that is, patients in whom PaO_2 is reduced). Oxygen relieves pulmonary vasoconstriction and right-heart strain and lessens myocardial ischemia, thereby improving cardiac output and oxygen delivery to the central nervous system and to other critical organs. In addition, a substantial amount of evidence supports the hypothesis that improved oxygen delivery to the lung enhances

pulmonary defenses and augments mucociliary transport. The major concern for most clinicians administering oxygen to patients with acute exacerbations of COPD is that oxygen supplementation will lead to hypercarbia and subsequent respiratory failure. Various mechanisms have been advanced to explain this observation, including depression of respiratory drive, alteration in ventilation–perfusion matching, and the Haldane effect (that is, the fact that oxygenated erythrocytes have a lower carrying capacity for CO_2 than deoxygenated erythrocytes).

On the basis of four observational studies, we conclude that oxygen administration in patients with acute exacerbations of COPD may result in hypercarbia but that the patients at highest risk for respiratory failure associated with oxygen administration can be identified (96–99).

A study of 23 patients with respiratory failure accompanying COPD who were given 28% oxygen demonstrated that PaCO_2 increased in 17 patients (mean increase, 4 mm Hg [range, –2 to 11 mm Hg]) (96). The authors stated that serious CO_2 retention was not encountered in any patients (external validity, 3 of 4 points; internal validity, 1b). A study of 7 patients with acute exacerbation who received both 24.5% and 28% oxygen demonstrated that PaCO_2 increased in 6 of 7 patients (99) (external validity, 3 of 4 points; internal validity, 1b). A study of 53 patients with acute exacerbations who received graded oxygen therapy to increase oxygen saturation had similar findings (98) (external validity, 1 of 4 points; internal validity, 2b). All but 3 patients had elevations in PaCO_2 ; the greatest increase was observed in patients who presented with the lowest PaO_2 . The largest study to address this issue enrolled 50 patients with acute exacerbations of COPD and administered 24% oxygen, followed by 28% oxygen if hypoxemia persisted (97) (external validity, 2 of 4 points; internal validity, 1b). Thirteen of the 50 patients (26%) developed hypercarbia and subsequently required mechanical ventilation. These 13 patients did not differ from the 37 who did not require mechanical ventilation in terms of age, results of baseline pulmonary function tests, or initial response to therapy. Of note, the relationship between arterial pH and PaO_2 at presentation was predictive of respiratory failure, but resting PaCO_2 was not. The authors derived a discriminant function for predicting respiratory failure ($\text{pH} = 7.66 - 0.00910$

[PaO₂]) that had a sensitivity of 77% (Figure). The authors showed that this predictive function was very useful in a validation cohort of 76 subsequent patients, 16 of whom (21%) required mechanical ventilation. Of these 16 patients, 13 had pH and PaO₂ values that intersected below the discriminant line (sensitivity, 81%). Although to our knowledge this predictive model is not heavily used, it emphasizes that patients with simultaneous hypercarbia and hypoxemia are at greatest risk for respiratory failure.

No available data directly address titration of oxygen following acute exacerbation of COPD. Perhaps the best data can be extrapolated from the Nocturnal Oxygen Therapy Trial, which found that 20% of 800 patients with acute exacerbation of COPD no longer required oxygen 3 weeks after hospital discharge (100).

2.3.5.1 Mucus Clearance Strategies: Expectorants, Mucolytics, and Mucokinetics

On the basis of five randomized, controlled trials involving five different drugs, we conclude that pharmacologic mucus clearance strategies have not been demonstrated to shorten the disease course of patients with acute exacerbations of COPD, although there is a possibility that these agents improve symptoms. There were no statistically significant differences reported in mean FEV₁ between treatments in any study. Regimens tested included domiodol compared with control (101) (external validity, 1 of 5 points; internal validity, 1 of 5 points); bromhexine compared with placebo (102) (external validity, 2 of 5 points; internal validity, 5 of 5 points); ambroxol compared with control (103) (external validity, 2 of 5 points; internal validity, 3 of 5 points); *S*-carboxymethylcysteine compared with bromhexine (104); (external validity, 3 of 5 points; internal validity, 4 of 5 points); and potassium iodide compared with chloramphenicol, physiotherapy, and placebo (89) (external validity, 2 of 5 points; internal validity, 1 of 5 points). Among five trials measuring subjective symptom scores for difficulty with expectoration, only two reported significant differences ($P < 0.01$ in favor of the mucolytic drug compared with control) (101, 103).

2.3.5.2 Mucus Clearance Strategies: Physical and Respiratory Therapies

On the basis of three randomized, controlled trials of chest physiotherapy and one observational study, we

conclude that mechanical percussion of the chest as applied by physical or respiratory therapists is ineffective and perhaps even detrimental in the treatment of patients with acute exacerbations of COPD. None of the randomized trials (105–107) reported any improvement in ventilatory function, either FEV₁ or FVC (external validity, 2 of 5 points, 3 of 5 points, and 2 of 5 points, respectively; internal validity, 1 of 5 points, 3 of 5 points, and 1 of 5 points, respectively). One trial described a significantly lower FEV₁ in patients who received chest percussion therapy compared with controls (106). A similar transient decrease in FEV₁ after chest percussion was previously described in an uncontrolled study (107). No other adverse effects were reported.

2.3.6 Noninvasive Positive-Pressure Ventilation

On the basis of five randomized, controlled trials and five observational studies, we conclude that noninvasive positive-pressure ventilation (NPPV) is a beneficial support strategy that decreases risk for invasive mechanical ventilation and possibly improves survival in selected hospitalized patients with respiratory failure (Table 11). In some of these studies, the exclusion criteria were omitted from the reports; in others, exclusion criteria included significant cardiovascular disease, lack of mental capacity, presence of pneumonia, and concern about upper airway narrowing or obstruction. Therefore, the selection criteria for this therapy remain unclear.

Four randomized, controlled trials compared NPPV with a standard-therapy control (109–112). Two trials found that need for intubation was significantly reduced in the NPPV groups (26% vs. 74% in a study involving 85 patients [111] and 9% vs. 67% in a study involving 23 patients [112]). A fifth trial comparing NPPV with a respiratory stimulant medication (doxapram) demonstrated a mortality benefit associated with NPPV; however, the benefit was not statistically significant (108). A meta-analysis published in 1996 (113), which included three of the four trials, three published abstracts (114–116), and one other published study (117), concluded that the risk for death was lower in patients who were randomly assigned to receive NPPV (odds ratio, 0.29 [CI, 0.15 to 0.59]). Patients receiving NPPV also had a lower risk for invasive mechanical ventilation (odds ratio, 0.20 [CI, 0.11 to 0.36]). The results of four prospective case series comparing NPPV-treated patients with historical controls were similar to those of the ran-

domized, controlled trials (118–121). One observational study (122) did not observe increased effectiveness of NPPV compared with more conventional treatment and found a large number of adverse effects associated with NPPV.

Additional questions addressed in the literature include comparisons between NPPV and invasive ventilation, optimal delivery methods for NPPV, and predictors of successful application of NPPV. Four randomized, controlled studies (123–126) compared types of NPPV delivery methods (external validity, 3 of 5 points, 1 of 5 points, 1 of 5 points, and 4 of 5 points, respectively; internal validity, 0 of 5 points, 1 of 5 points, 1 of 5 points, and 2 of 5 points, respectively). Outcomes of interest were effect on gas exchange, need for intubation, mortality, adverse effects or side effects, and comfort of the devices. No significant differences in these variables were seen among the different modes of ventilation. A retrospective study attempting to identify variables that could predict a successful outcome of NPPV looked at anthropometric and demographic characteristics, nutritional status, spirometry, blood gases, and causes of acute exacerbation of COPD. Factors that predicted success included higher pH, lower PaCO₂, and higher FVC ($P < 0.05$). Poor outcomes were associated with a diagnosis of pneumonia, poor nutritional status, and decreased adherence to the apparatus protocol (127–129).

3.0 RESEARCH PRIORITIES

Chronic obstructive pulmonary disease is thought to cause 5% of all deaths in the United States, enormous disability, and \$18 billion in annual health costs. Therefore, the paucity of primary data on therapeutics is startling. We found that in more than 40 years of research, fewer than 1100 patients had been enrolled in randomized, placebo-controlled trials of antibiotics, fewer than 650 patients had been enrolled in studies comparing corticosteroids with placebo (before the 1999 SCOPPE trial, the count was less than 400), and virtually no controlled trials have enrolled patients with milder (out-patient) exacerbations. Certainly, more in-depth research into therapeutics and management would greatly benefit patients with this disease.

To be maximally beneficial, however, more groundwork is required. At present, we lack a reproducible,

transportable definition of *acute exacerbation*, and we also lack an objective rating system for severity. Equally important, there is no consensus on the outcomes that should be measured and reported in clinical studies, although there is an emerging recognition that nonphysiologic outcomes, such as symptoms, quality of life, and interval before subsequent relapse, are important to patients. Our first research objectives must include untangling the questions surrounding selection of patients for antibiotic and corticosteroid treatment, identifying optimal dosing and durations for these agents, and determining the degree to which broad- and narrow-spectrum antibiotics have similar efficacy.

In addition, there are many potentially promising new directions to be explored. Researchers may consider examining the components of mucus formation, content, release, and transport; strategies for improving muscle strength and reducing muscle fatigue; therapies aimed at aborting the exacerbation cycle, including arrest of the inflammatory cascade; strategies aimed at preventing infectious exacerbations, perhaps through reducing bacterial adherence or limiting cellular damage in the presence of microorganisms; and determination of biological markers of infection and inflammation (for example, antielastase, antioxidants, cytokine release or action) in the blood, sputum, or both.

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