Management of Acute Exacerbations of COPD : A Summary and Appraisal of Published Evidence

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special report

Management of Acute Exacerbations of COPD*

A Summary and Appraisal of Published Evidence

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Study objectives: **To critically review the available data on the diagnostic evaluation, risk stratification, and therapeutic management of patients with acute exacerbations of COPD.**
Design, setting, and participants: **English-language articles were identified from the following databases: MEDLINE (from 1966 to week 5, 2000), EMBASE (from 1974 to week 18, 2000), HealthStar (from 1975 to June 2000), and the Cochrane Controlled Trials Register (2000, issue 1). The best available evidence on each subtopic then 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. Study design and results were summarized in evidence tables. Individual studies were rated as to their internal validity, external validity, and quality of study design. Statistical analyses of combined data were not performed.**
Measurement and results: **Limited data exist regarding the utility of most diagnostic tests. However, chest radiography and arterial blood gas sampling appear to be useful, while short-term spirometry measurements do not. In terms of the risk of relapse and the risk of death after hospitalization for an acute exacerbation, there are identifiable clinical variables that are associated with these outcomes. Therapies for which there is evidence of efficacy include bronchodilators, corticosteroids, and noninvasive positive-pressure ventilation. There is also support for the use of antibiotics in patients with more severe exacerbations. Based on limited data, mucolytics and chest physiotherapy do not appear to be of benefit, and oxygen supplementation appears to increase the risk of respiratory failure in an identifiable subgroup of patients.**
Conclusions: **Although suggestions for appropriate management can be made based on available evidence, the supporting literature is spotty. Further high-quality research is needed and will require an improved, generally acceptable, and transportable definition of the syndrome "acute exacerbation of COPD" and improved methods for observing and measuring outcomes.**

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Abbreviations: ACCP = American College of Chest Physicians; ACP = American College of Physicians; APACHE = acute physiology and chronic health evaluation; ASIM = American College of Physicians-American Society for Internal Medicine; CI = confidence interval; CXR = chest radiograph; EV = external validity; Exp = experimental; MDI = metered-dose inhaler; NPPV = noninvasive positive-pressure ventilation; Obs = observational; PEFR = peak expiratory flow rate; RCT = randomized controlled trial; SCCOPE trial = Systemic Corticosteroids in COPD Exacerbations trial

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This article describes the background evidence for the clinical practice guidelines entitled "The Evidence Base for Management of Acute Exacerbations of COPD." A joint panel from the American College of Physicians (ACP)-American Society for Internal Medicine (ASIM) and the American College of Chest Physicians (ACCP) assisted in the design, conduct, and development of this summary, which is based in large part on the evidence report produced by the Evidence-Based Practice center at Duke University, Durham, NC.[1]

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The primary aims of this article are to summarize and evaluate the published data addressing the care of patients with acute exacerbations of COPD and to improve the care that these patients receive by identifying efficacious and inefficacious treatment strategies. We first review the health impact of COPD. We then define the entity *acute exacerbation* and describe the methods that we used to identify and grade the available data on the care of patients with this condition. In the "Results" section, 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 therapeutic agents such as oxygen and corticosteroids. Last, we comment on domains of management for patients with acute exacerbations that would most benefit from further research.

COPD

In the United States at present, > 16 million adults are afflicted with COPD, a slowly progressive condition that typically becomes symptomatic in the fifth and sixth decade of life. As the US population ages, the prevalence of this disease is expected to climb.[2] COPD 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 direct health-care costs of $18 billion.[3,4]

The term COPD is used to describe a range of pathophysiologic entities that are characterized by airflow obstruction, including chronic bronchitis, emphysema, asthma, and bronchiectasis. In this article, and in our guidelines, we focus our attention on the care of patients with the chronic bronchitis and emphysema, an approach consistent with the National Heart, Lung, and Blood Institute 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 the 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 intermittent airway inflammation that leads to frequent, prolonged episodes of productive cough. In contrast, 15% of patients with COPD suffer primarily from emphysema, a disease in which destruction of the infrastructure of alveoli and distal airspaces, and thus the portion of the lung that provides elastic recoil, occurs. Both conditions predispose patients to a common constellation of symptoms and signs, and to a collection of derangements in respiratory function.

Spirometric testing is used to confirm the diagnosis of COPD. Typical abnormalities include a decrease in FEV_1 and a decrease in the ratio of FEV_1 to FVC. Other abnormalities include an increased residual volume and total lung capacity, and a limited and incomplete response in FEV_1 to bronchodilators (incomplete reversibility). A diminished diffusing capacity of the lung for carbon monoxide is often seen in patients with emphysema, and a response to bronchodilators can be seen in patients with concomitant asthma. Several staging systems are available for patients with stable COPD. Both the European Respiratory Society and the American Thoracic Society systems use FEV_1, which correlates most closely with mortality and frequency of acute exacerbation, as the sole staging characteristic. The British Thoracic Society staging definition also includes clinical features of a patient's cough, sputum, dyspnea, and lung sounds (Table 1).

What Is an Acute Exacerbation of COPD?

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. Unfortunately, many definitions exist, many authors employ substantively different criteria, and many studies

Table 1—*Available Staging Systems for COPD

Staging Systems	Staging Systems for Stable COPD		
	Mild	Moderate	Severe
Stable COPD			
ERS guidelines[109]			
FEV_1	≥ 70%	50–69%	< 50%
ATS 1995 guidelines[110]			
FEV_1	≥ 50%	35–49%	< 35%
BTS Guidelines[111]			
FEV_1	60–79% predicted	40–59% predicted	< 40% predicted
Cough	Smoker's cough	Cough (± sputum)	Prominent
Dyspnea	Minimal	On exertion	On exertion or at rest
Lung examination findings	N1	± wheeze	Hyperinflation, wheeze
Other examination findings	N1	N1	Cyanosis, edema
Acute exacerbations of COPD			
Type 3	1 of 3 symptoms† as well as 1 of the following: upper respiratory tract infection in past 5 d, fever without other apparent cause, ↑ wheezing, ↑ cough, and ↑ respiratory rate or heart rate by 20% above baseline		
Type 2		2 of 3 symptoms†	
Type 1			All 3 symptoms†

*N1 = normal; ↑ = increase; ↓ = decrease; ERS = European Respiratory Society; ATS = American Thoracic Society; BTS = British Thoracic Society.

†Cardinal symptoms of acute exacerbations of COPD: worsening of dyspnea; increase in sputum purulence; and increase in sputum volume.[6]

poorly describe their inclusion criteria. As a generalization, however, most published definitions embrace some combination of the following 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 the severity of an acute exacerbation. Probably the most commonly used system was developed by Anthonisen and colleagues[6] and is based on these and other symptoms. Patients with type 1 (severe) exacerbations have all three of the above symptoms, and those with type 2 (moderate) exacerbations have two of three of the symptoms. Patients with type 3 (mild) exacerbations have at least one of these symptoms, as well as one of the following clinical criteria: an upper respiratory tract infection in the past 5 days; fever without another apparent cause; increased wheezing; increased cough; or increase in respiratory rate or heart rate by 20% above baseline (Table 1).[6] 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 exists regarding the nature of the infectious agent, as well as its exact role. Sputum obtained from patients with mild to moderately severe chronic bronchitis routinely grow a variety of bacteria in cultures, including *Haemophilus influenzae* (22%), *Pseudomonas aeruginosa* (15%), *Streptococcus pneumoniae* (10%), and *Moraxella catarrhalis* (9%).[7] Nonpathogenic bacteria, such as *Haemophilus parainfluenzae*, account for up to one third of all isolates. Also, the following certain groups of patients are more likely to be colonized with resistant organisms such as Pseudomonas: patients from nursing homes; patients recently treated with antibiotics; and patients admitted to ICUs. The role of these colonizers in the pathogenesis of acute exacerbation remains unclear, and their presence makes the interpretation of any sputum culture difficult. Some investigators[8–10] also have proposed that *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* may precipitate between 1% and 10% of exacerbations, and others[11,12] have pointed out that the presence of eosinophilic inflammation in bronchial biopsy specimens of patients with exacerbations is consistent with viruses (notably rhinovirus) playing an important role.

Acute exacerbations are clearly associated with environmental exposures as well, as significant correlations between levels of respirable particles (diameter, < 10 μm) and ozone have been linked to hospital admission rates.[13] Finally, severe exacerbations may be precipitated by other serious clinical conditions, such as heart failure, nonpulmonary infections, pulmonary embolism, and pneumothorax.[14]

The outcomes of COPD exacerbations are similarly heterogeneous. While nearly 50% of exacerba-

tions are not reported to physicians,[15,16] exacerbations requiring hospitalization are associated with an inpatient mortality of 3 to 4%.[17] For those patients requiring treatment in an ICU for an acute exacerbation, mortality rates are substantially higher (in hospital, 11 to 24%; by 1 year, 43 to 46%). [14,18–21] After an acute exacerbation, most patients are expected to experience at least a temporary decrement in functional status and quality of life,[16,22,23] and half of those patients who are hospitalized are expected to be readmitted at least once in the ensuing 6 months.[14,24]

Materials and Methods

Identification of Topics for Literature Search

Topics to be covered in this article 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 (Durham, NC). The topic list was generated to address the following 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?; and (3) what information is available to help guide clinicians in using available therapies and interventions? In this article, we do not consider the care of patients in stable condition with chronic COPD, experimental (Exp) therapies that are not widely available, or the provision of invasive mechanical ventilation.

Search Strategy

The information presented in this report was gathered through systematic searches and ongoing surveillance of the MEDLINE (from 1966 to week 5, 2000), EMBASE (from 1974 to week 18, 2000), and HealthStar (from 1975 to June 2000) databases and of the Cochrane Controlled Trials Register (2000, issue 1). Search strategies included index terms and text words for "COPD" and "acute exacerbation" and specific terms relating to the interventions and outcomes discussed in ensuing sections. 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, appropriate articles were retrieved, and the reference lists of those were examined. Seven hundred seven full-text articles were obtained through this process, and those that were eligible for analysis were summarized in evidence tables. The data, study methods, and evidence available in each article then were evaluated in the manner described below.

Assessment of the Quality of Available Evidence

Each retrieved study was evaluated along the following two dimensions: to what extent did the study enroll the patients in whom we were interested (*external validity* [EV])?; and to what extent did the study follow the optimal design (*internal validity*)? Our criteria for EV hinged on the following two questions: did the study enroll patients who had COPD by a conventional definition (Table 1)?; and did the study enroll patients with acute exacerbations of COPD, as documented both by a description of the cohort symptomatology and by a description of the diagnostic testing that was used to exclude other etiologies? We generated a scoring system for EV (Table 2) that ranged from 0 (poorest quality) to 5 (highest quality) based on the adequacy of the documentation of each study for these two concerns. Sample size was not taken into consideration, and all comments about the "significance" of results reflect that the authors reported statistical significance at the $p < 0.05$ level.

Our criteria for internal validity differed when we evaluated Exp vs observational (Obs) studies. To evaluate Exp studies, we employed the scoring system described by Jadad and colleagues[25] that assigns scores based on the quality of design of randomized controlled trials (RCTs) (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 Obs studies, we used the hierarchy of evidence proposed by Ball et al[26] (Table 4). Unlike the Jadad scale for Exp designs, lower scores for the internal validity of Obs 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 reported using the system proposed by Justice and colleagues[27] (Table 5). This scoring system ranges from 0 to 5; higher scores reflect that the prediction model presented in the article has been more extensively evaluated on independent populations of patients.

For studies that appear in the tables, these scores are recorded in those tables. For studies that are referenced only in the text, these assessments are recorded in parentheses the first time the study is mentioned in the following manner. EV is documented as a ratio of the total number of points earned to the number of points possible (*eg*, 3:5 [Table 2]). For internal validity, the type of study (Exp or Obs) is documented, followed by the score on the relevant scale (see Tables 3 and 4). The degree of validation of prognostic models is relevant only to the studies presented in Tables 7 and 8, and are reported there.

Choice of Inclusion of Studies for Reporting and Analysis

The minimum threshold for inclusion of studies of different design types 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 for some

Table 2—*EV Scale

Scale	Criteria
1	Validity of the underlying COPD diagnosis A. COPD diagnosis based on spirometry[109] B. Baseline stable ventilatory status (*eg*, FEV_1) of study population described
2	Validity of diagnosis of acute exacerbation of COPD. Definition of acute exacerbation includes at least 2 of the following: increased sputum purulence; increased sputum volume; increased dyspnea
3	Characterization of severity of acute exacerbation of COPD. Study describes the severity at enrollment based on at least 2 of the following: mental status change; work of breathing (*ie*, respiratory rate or use of accessory muscles); ventilatory status (*ie*, FEV_1 or PEFR; P_{CO_2} and either O_2 saturation or P_{O_2})
4	Duration of follow-up (treatment articles only); outcomes assessed at ≥ 24 h

*For each set of criterion: Yes = 1, No = 0.

Table 3—*Internal Validity Scale (Exp Studies)

1. Was the study described as randomized?
   1 = Yes
   0 = No
2. Was the method of randomization well described and adequate?
   0 = not described
   1 = described and adequate
   −1 = described, but not adequate
3. Was the study described as double-blind?
   1 = Yes
   0 = No
4. Was the method of double-blinding well described and adequate?
   0 = not described
   1 = described and adequate
   −1 = described, but not adequate
5. Was there a description of withdrawals and dropouts sufficient to determine the number of patients in each treatment group entering and completing the trial?
   1 = Yes
   0 = No

*Adapted from Jadad et al.[25]

treatment and diagnostic modalities, information from these types of studies was either scanty or lacking. Ultimately, we chose a different threshold of inclusion for each topic based on the availability of relevant data (Table 6). The varying quality of the assessed studies is taken into account in the evaluation.

Approach to the Patient With an Acute Exacerbation of COPD

In the following section, we discuss our recommendations and findings for the following three domains of care for patients with acute exacerbations of COPD: risk stratification of patients (specifically, data on predictors of outpatient relapse) and predictors of 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 methodological 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. As such, many studies designed to evaluate one intervention include patients receiving other interventions, and these cointerventions make analysis of the effects of single therapies more difficult, especially when cointerventions are not standardized. Second, many studies evaluate changes in FEV_1 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 both to other quantitative measures (such as arterial blood gas values) and to qualitative evaluations of symptoms.[15,28] Last, the majority of studies that we found address the care of patients in emergency departments or inpatient settings, while many patients with milder acute exacerbations do not receive care in these settings. As such, our conclusions are more focused on the care of patients with more severe exacerbations.

Risk Stratification

Prediction of Outpatient Relapse

Based on 10 studies that evaluated patients with acute exacerbations of COPD in emergency departments (7 studies) and in the outpatient setting (3 studies), we concluded that certain characteristics are associated with patients returning for more treatment rather than with those experiencing gradual improvement (Table 7). The ability to identify patients at high risk for relapse should improve decisions about hospital admissions and follow-up appointments. Several investigators have confirmed that patients who have lower pretreatment or posttreatment FEV_1 levels, who receive more bronchodilator treatments or corticosteroids during their visit or have higher rates of prior relapse, are more likely to return (*ie*, relapse) than are patients with more favorable values of these characteristics. At present, the available prediction models can provide clinical guidance based on these identified predictors, and those patients with these characteristics are at higher risk of relapse. It should be noted that these models, however, show only moderately good discriminatory power. For example, the best model derived to predict relapse (defined as a return to the emergency department within 14 days of initial presentation) had a sensitivity of 0.57 and a specificity of 0.72.[29]

Prediction of Inpatient Mortality

Based on 11 studies, we concluded that certain physiologic characteristics are associated with a higher likelihood of inpatient mortality. Prediction models containing these characteristics are potentially useful for risk stratification in the context of population-based and randomized studies. To the extent that these characteristics are used to influence decisions about instituting, continuing, or withdrawing life-sustaining therapies, caution should be exercised. We identified no prediction models that were able to identify patients who were virtually certain to die (for example, those with a likelihood of death of $\geq 90\%$) during their inpatient stay. It should be noted also that in these studies, there is substantial

Table 4—*Internal Validity Scale (Obs Studies)

Grade of Recommendation	Level of Evidence	Prognosis	Diagnosis
A	1a	SR (with homogeneity†) of inception cohort studies; or a CPG validated on a test set.	SR (with homogeneity) of level 1 diagnostic studies; or a CPG validated on a test set
	1b‡	Individual inception cohort study with ≥ 80% follow-up	Independent blind 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
B	2a	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity) of level ≥ 2 diagnostic studies
	2b§	Retrospective cohort study or follow-up of untreated control patients in an RCT; or CPG not validated in a test set.	Independent blind comparison but either in nonconsecutive patients or confined to a narrow spectrum of study individuals (or both), all of whom have undergone both the diagnostic test and the reference standard; or a diagnostic CPG not validated in a test set
	2c	"Outcomes" research	
	3		Independent blind comparison of an appropriate spectrum, but the reference standard was not applied to all study patients
C	4	Case-series (and poor quality prognostic cohort studies‖)	Reference standard was not applied independently or not applied blindly
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"

*Adapted from Centre for Evidence-Based Medicine.[26] SR = systematic review; CPG = clinical practice guidelines; SpPin = diagnostic finding the specificity of which is so high that a positive result rules in the diagnosis; SnOut = diagnostic finding the sensitivity of which is so high that a negative result rules out the diagnosis.

†*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.

§Inception cohort studies with < 80% follow-up and retrospective studies were included in this category.

‖Poor quality prognostic cohort studies include ones in which sampling was biased in favor of patients who already had the target outcome, or in which the measurement of outcomes was accomplished in < 80% of study patients, or in which outcomes were determined in an unblinded, nonobjective way, or in which there was no correction for confounding factors.

Table 5—*Degree of Validation of Predictive Models*

Level	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—*Inclusion Thresholds by Topic*

Topic	Minimum Study Design Included
Diagnosis/prognosis	Cohort design
Mucus clearance strategies	Randomized, placebo-controlled
Bronchodilating agents	Randomized, agent-to-agent comparisons
Corticosteroids	Randomized, placebo-controlled
Antibiotics	Randomized, placebo-controlled
Oxygen therapy	Obs cohort
NPPV	Randomized, controlled; Obs cohort

variability in the inclusion criteria, raising concerns about the EV of some of these results. Of the 11 studies, 8 (Table 8) documented an association between specific clinical predictors and mortality, while the other 3 studies did not report significant

Table 7—*Predictors of Relapse Analyzed in More Than One Study

Predictors	Fedullo et al[112]/ 1986 (n = 24)	Murata et al[113]/ 1989 (n = 268)	Emerman et al[114]/ 1991 (n = 83)	Murata et al[115]/ 1991 (n = 352)	Murata et al[29]/ 1992† (n = 289)	Murata et al[29]/ 1992 (n = 213)	Ball et al[116]/ 1995 (n = 471)	Parshall[117]/ 1999 (n = 239)	Adams et al[118]/ 2000 (n = 173)‡	Dewan et al[119]/ 2000 (n = 107)§
Patient demographics										
Older age	−		+		−	−	−	−	−	−
Female sex			+				−		−	
Smoking history			−				−		−	
Clinical characteristics										
↑ Body temperature	+			−	−					
↑ Heart rate	−			−	−					
↑ Respiratory rate	−			−	−					
↑ WBC count	−		−	−						
Hypertension									−	−
Diabetes									−	−
Liver disease									−	−
Chronic renal failure									−	−
Heart disease/heart failure							+		+	−
Pulmonary function tests										
% Recovery of FEV_1				−		−				
$PaCO_2$ ↑	+		−	−						
PaO_2 ↓	+		−	−						
pH ↓	+		−	−						
Posttreatment FEV_1 ↓			−	+		+				
Pretreatment FEV_1 ↓			+	+		−				+
Severity of exacerbation							−		−	
Abnormal findings on auscultation	−						−			
ED timing and visits										
Admission rate of previous visits ↑					−	+				
Previous visit within 7 d					+	−				
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		−	−	−	−					
Number of bronchodilator treatments ↑			+	+	+			−	−	
Oral prednisone at entry				−	−					
No oral prednisone at discharge				+	+					
Steroid treatment in ED			−	−	−				−	
INTV	2b	2b	1b	2b	2b	2b	1b	1b	4	2b
EV‖	1	2	2	4	2	2	1	0	3	2

*ED = emergency department; INTV = internal validity; + = statistically significantly associated with relapse; − = not statistically significantly associated with relapse. See Table 1 for abbreviations not used in text. Degree of validation of model is zero in all cases.

†Murata et al[29] and Murata et al[115] contain partially overlapping study populations.

‡Three hundred sixty-two patient visits were analyzed from a sample of 173 patients.

§Two hundred thirty-two exacerbations were analyzed from a sample of 107 patients.

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

Table 8—*Statistically Significant Predictors of Inpatient Mortality

Study/yr	Setting	Analysis	N	Validity			Significant Predictors of Mortality†
				Ext	Int	Degree of Validation	
Connors et al[21]/1981	ICU	Multi	1,016	1	1b	3	↑ APS ↓ BMI ↑ Age ↓ ADL ↓ PaO_2/FIO_2 ratio Absence of comorbid CHF ↓ Serum albumin Absence of comorbid cor pulmonale
Seneff et al[20]/1995	ICU	Multi	362	1	1b	0	↑ Nonrespiratory APS score ↑ No. of pre-ICU hospital days
Burk and George[18]/1973	Hospital ward/ICU	Uni	74	1	2b	0	Use of mechanical ventilation (vs conservative care) General medical ward care (vs ICU care) CHF as etiology of ARF (vs respiratory infection)
Warren et al[120]/1980	Hospital ward	Uni	135	2	2b	0	↑ Age Highest level of arterial $PaCO_2$ during controlled oxygen therapy Lowest pH < 7.26 ($p < 0.025$)
Jeffrey et al[121]/1992	Hospital	Uni	95	2	1b	2	*Measured at admission* ↑ blood urea concentration ↓ systolic BP ↓ arterial pH *Measured throughout hospital stay* Lowest pH < 7.26 Lowest pH < 7.28
Heuser et al[122]/1992	ICU	Multi	3,050	0	2b	0	↑ Age Primary diagnosis pneumonia (vs asthmatic bronchitis) MedisGroups Admitting severity group 3 or 4
Portier et al[19]/1992	ICU	Multi	322	1	1b	0	Presence of cachexia ↓ Serum sodium Required mechanical ventilation in first 24 h Not COPD as underlying chronic respiratory insufficiency Previous confinement to home Presence of edema
Fuso et al[123]/1995	Hospital	Multi	590	3	2b	0	↑ Age $P(A\text{-}a)O_2 > 41$ mm Hg Presence of atrial fibrillation Presence of ventricular arrhythmias

*Ext = external; Int = internal; Multi = multivariate; Uni = univariate; $P(A\text{-}a)O_2$ = alveolar-arterial oxygen pressure difference; BMI = body mass index; ADL = activities of daily living; CHF = chronic heart failure; APS = acute physiology score; ARF = acute respiratory failure.
†Presence of predictor in noted direction is associated with an increased risk of mortality.

predictors.[17,30,31] The two largest studies examining this outcome are summarized below.

The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments enrolled 1,016 patients with acute exacerbations of COPD on hospital admission.[14] The patients had a variety of etiologies for exacerbation, including respiratory tract infection (including pneumonia) (48%), congestive heart failure (26%), lung cancer (3.3%), pulmonary embolus (1.4%), and pneumothorax (1%). The outcome of interest was mortality by 180 days, which was 33% (2-year mortality, 49%). Significant predictors were worse acute physiology score from the acute physiology and chronic health evaluation (APACHE) III algorithm,[32] lower body mass index, older age, worse functional status 2 weeks before hospital admission, lower PO_2/fraction of inspired oxygen ratio, history of congestive heart failure, lower serum albumin level, presence of cor pulmonale, lower activities of daily living scores, and lower Duke activity status index score. Predictions from the model that included these variables showed good calibration (calibration index, 0.0016) and fair discrimination (area under receiver operating characteristics curve, 0.731) in a validation cohort.

Another large prospective cohort study enrolled

362 patients who were admitted to ICUs with respiratory failure because of COPD. Patients with pneumonia, pulmonary edema, or pulmonary embolus were excluded. The in-hospital mortality of 23.8% was predicted by the number of pre-ICU hospital days and the *nonrespiratory* component of the APACHE III score. A separate analysis identified the following three predictors of 180-day mortality: acute physiology score; old age; and a higher number of pre-ICU hospital days. Activities of daily living were also a significant predictor on univariable analysis.[20]

Diagnostic Testing

General Approach

Many assessment techniques frequently are used in evaluating patients with acute exacerbations of COPD. These include measuring routine laboratory values, performing a physical examination, obtaining an ECG, assessing cardiac function, and instituting an empiric trial of diuretics. We found no published evidence that could help us to determine the utility of these approaches. For another commonly used assessment (arterial blood gas sampling), we found indirect evidence in a number of studies supporting 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 those patients currently in need of oxygen therapy and those potentially requiring mechanical ventilatory support. Two other diagnostic modalities, chest roentgenography and spirometric testing, have been assessed and are discussed below.

Chest Roentgenography in Establishing Causes/ Coexisting Illnesses in Acute Exacerbation of COPD

Based on three Obs studies, we concluded that for patients treated in emergency departments or hospitals, a chest radiograph (CXR) is a useful diagnostic test. A substantial rate of CXR abnormalities was documented in the following two retrospective studies: 16% abnormality rate from a study of 685 episodes occurring in a single urban emergency department (EV, 0/4; internal validity, Obs 2b)[33]; and 16% (7% judged as "clinically significant") occurring in 107 patients admitted to a single hospital (EV, 0/4; internal validity, Obs 2b).[34] In a prospective cohort study of 128 hospital admissions for asthma or COPD, 21% of patients had a change in management that was prompted by their CXR result (the majority of these patients had new pulmonary infiltrates or evidence of congestive heart failure) (EV, ¼; internal validity, Obs 1b).[35] Models presented by these authors for predicting CXR abnormalities were not sufficiently reliable to be clinically useful.

Spirometric Testing

Although several studies have shown that FEV_1 is loosely correlated with relapse rate, based on three Obs studies, we concluded that spirometric assessment at the time of presentation or during the course of treatment is of limited usefulness in the care of patients with acute exacerbations of COPD. Changes in clinical status do not correlate well, in general, with changes in spirometric measures in patients with this disease. A study performed in one urban emergency department (EV, 3:4; internal validity, Obs 1b) enrolling 70 patients demonstrated that FEV_1 at the time of presentation was weakly, but statistically significantly, correlated with both P_{CO_2} ($r = -0.46$; $p < 0.001$) and pH ($r = 0.33$; $p < 0.01$) but was uncorrelated with arterial P_{O_2}. These results are different from those seen in studies of patients with asthma presenting to the emergency department, in which spirometry and arterial blood gas levels are highly correlated.[36] Another study enrolling 199 patients presenting with acute exacerbation of COPD in an urban emergency department demonstrated that peak expiratory flow rate (PEFR) and FEV_1 are correlated ($r = 0.84$; $p < 0.001$); the clinical implication of this finding, however, is unclear (EV, 1:4; internal validity, Obs 1b).[37] This latter study also noted that for a minority of patients, the absolute difference between the percent predicted values based on FEV_1 and those based on PEFR was $> 10\%$.

Therapeutic Interventions

Bronchodilating Agents

Based on 14 randomized studies, we concluded the following: that short-acting β-agonist-type and anticholinergic-type inhaled bronchodilators have comparable effects on spirometry and a greater effect than all parenterally administered bronchodilators (*ie*, parenteral methylxanthines and sympathomimetics); that the toxicity profile of the methylxanthine agents makes them potentially harmful; and that there may be an additional benefit in some patients when a second bronchodilating agent is administered once the maximal dose of the initial inhaled bronchodilator is reached. These generalizations are limited by the small number of analyzable trials[38,39] that have been published, the substantial differences in inclusion and exclusion criteria between them, and the variability in drug dosages that were studied.

Efficacy of Bronchodilators: There were five RCTs that compared individual bronchodilating agents. Two RCTs[39,40] compared the efficacy of inhaled ipratropium bromide to that of short-acting β-agonists (EV, 2:5; internal validity, Exp 3:5[39]; EV, 3:5; internal validity, Exp 5:5[40]). The first study enrolled 40 patients and observed that FEV_1 among those receiving ipratropium showed statistically significant improvement from day 1 to day 7 at 15 and 30 min after administration, while no significant differences were seen at 0, 5, 10, 60, 120, and 240 min after administration. Similarly, the only significant improvement observed in patients receiving fenoterol was at 60 min after treatment on day 7 ($p < 0.05$).[39] The second study involved 32 patients in a crossover design comparing ipratropium and metaproterenol. At 30 min after administration, patients receiving ipratropium had a significant rise in Pao_2, while those receiving metaproterenol had a significant fall in Pao_2. At 90 min, these differences had disappeared, and both patient groups showed a significant improvement in FEV_1. However, no additional improvement was seen after the patients were crossed over to treatment with the second drug.[40] In a study of 90 patients with asthma and/or COPD during transport to an emergency department, treatment with nebulized albuterol was compared to treatment with subcutaneous terbutaline. Patient-perceived improvement, respiratory rate, and dyspnea rating showed significant improvements only in the group receiving albuterol ($p < 0.05$) (EV, 0:5; internal validity, Exp 5:5).[41] In a dosing study[42] involving 86 patients, there were no significant differences in FEV_1 at 2 h between patients receiving nebulized albuterol, 2.5 mg, given every 20 min and those receiving nebulized albuterol, 2.5 mg, given every hour, although there was a suggestion that patients with lower FEV_1 benefited from the former regimen (EV, 1:5; internal validity, Exp 4:5).

Incremental Benefit of a Second Bronchodilator: The addition of a methylxanthine to inhaled bronchodilators was examined in three randomized studies. One study[43] involving 143 patients with asthma and COPD receiving care in an emergency department reported a trend toward lower hospitalization rates for patients given aminophylline in addition to short-acting β-agonists and corticosteroids (EV, 1:5; internal validity, Exp 3:5). Two studies[44,45] found no significant differences in measured changes in FEV_1 between patients receiving standard therapy (including short-acting β-agonists) and those who also received aminophylline (EV, 4:5; internal validity, Exp 5:5[44]; EV, 1:5; internal validity, Exp 4:5[45]). The effect of adding a second class of bronchodilator (*ie*, anticholinergic or short-acting β-agonists) to a full-dose regimen of the other agent has been examined in seven randomized studies. Six of these studies[38,46–50] specifically examined the impact of an anticholinergic added to a short-acting β-agonist for treatment of acute exacerbations of COPD. In a study[46] of 57 emergency department patients, the addition of glycopyrrolate to albuterol resulted in a proportionally larger increase in FEV_1 than that experienced by patients treated with albuterol alone. (EV, 2:5; internal validity, Exp 4:5). A study[47] of 68 emergency department patients found that the addition of ipratropium to isoetharine resulted in significantly lower lengths of stay but that admission rates to the hospital were similar (EV, 1:5; internal validity, Exp 5:5). Three other studies[38,48,49] were unable to detect a difference in spirometry (FEV_1 and/or FVC) in patients treated with short-acting β-agonists alone when compared to those who also were given anticholinergic agents (EV, 3:5; internal validity, Exp 4:5[48]; EV, 1:5; internal validity, Exp 2:5[38]; and EV, 1:5; internal validity, Exp 4:5[49]). A three-armed study[50] examined 52 emergency department patients receiving a short-acting β-agonist alone (fenoterol), an anticholinergic alone (ipratropium), or both agents. At 90 min, patients in all three groups experienced similar improvements in FEV_1. Patients receiving ipratropium alone had the lowest rate of reported side effects (EV, 2:5; internal validity, Exp 5:5).

Adverse Effects: The adverse effects of bronchodilators are varied. The side effects of ipratropium bromide are generally fewer and milder. Three RCTs[39,47,49] did not report any adverse effects with ipratropium bromide. Other effects include increased incidence of tremors and dry mouth,[40,50] and urinary retention when used in combination with albuterol.[48] The adverse effects of albuterol include tremors, headache, nausea, vomiting, and palpitations. Adverse cardiovascular effects such as changes in heart rate, BP, and ECG tracings are also possible but rare.[51] Adverse effects associated with theophylline include nausea, vomiting, headache, arrhythmias, and seizures.[44,52] The effects are more significant among those patients with higher levels of theophylline.

Bronchodilating Agent Delivery Devices

Based on eight RCTs[53–60] comparing metered-dose inhalers (MDIs) and nebulizers in patients with acute exacerbations of COPD, we concluded that there is insufficient evidence to support the conclusion that one delivery modality is superior to the other. Of the eight studies, six[53–55,57,59,60] described using spacer devices with the MDIs, one[56] specifi-

Table 9—*Randomized Trials of Corticosteroid Agents

Study/yr	Sample Size	Corticosteroid Agent	Equivalent Day 1 Dosage of Methylprednisolone, mg	End Point	Steroid vs Placebo	Steroid Over Time	Validity
Bullard et al[63]/1996	138	Hydrocortisone (100 mg IV once)	20	↑ FEV_1 from 0–6 h		+†	External 1:5 Internal 4:5
Davies et al[66]/1999	56	Prednisolone (30 mg po daily for 14 d)	37.5	↑ Mean % predicted prebronchodilator FEV_1	+	+†	External 4:5 Internal 5:5
				↑ Mean % predicted postbronchodilator FEV_1	+	+†	
				↓ Length of stay	+†		
Thompson et al[65]/1996	27	Prednisone (60 mg po daily for 3 d, then tapered)	75	↑ Mean slope of FEV_1	+†		External 5:5
				% Change in FEV_1 from day 1 to day 10	+†		Internal 3:5
Emerman et al[64]/1989	100	Methylprednisolone (100 mg IV once)	100	↓ Length of stay	−		External 3:5
				↑ FEV_1 (% improvement)	−	+NR	Internal 4:5
				Hospital admission rate	−		
Albert et al[62]/1980	44	Methylprednisolone (35 mg [based on 0.5 mg/kg] IV every 6 h for 3 d)	140	↑ FEV_1 (% change prebronchodilator)	+†		External 4:5 Internal 5:5
				↑ FEV_1 (% change postbronchodilator)	+†		
Niewoehner et al[67]/1999	271	Methylprednisolone (125 mg IV every 6 h for 3 d, followed by po prednisone taper)	500	↓ Length of stay	+†		External 2:5
				↑ FEV_1 at days 1, 2, and 3	+†		Internal 4:5

*NR = not reported; + = beneficial effect of corticosteroid; − = beneficial effect of placebo.
†Significance at $p < 0.05$ level.

cally mentioned using an MDI without a spacer, and one (an abstract)[58] did not describe whether or not a spacer was used. The percentage improvement in the FEV_1 was significantly larger after treatment with the nebulizer than with the MDI in two studies[57,58] but was not significantly different in the other six.[53–55,56,59,60] A meta-analysis[61] of bronchodilator delivery devices in acute airflow obstruction included these studies of COPD and additional studies of patients with asthma. The meta-analysis found a negligible effect of nebulizers vs MDI that is neither clinically nor statistically significant. The doses of the bronchodilator administered by MDIs in these studies were lower than those delivered by nebulizer and were lower than those often used in clinical practice, and, thus, the few positive results may reflect differences in the dose of the bronchodilator actually received. Furthermore, the studies were all rather small, resulting in imprecise estimates of the efficacy of MDI vs nebulizer delivery.

Corticosteroid Drugs

Based on six randomized, placebo-controlled studies, we concluded that a short course of systemic corticosteroid therapy given to patients with acute exacerbations of COPD improves spirometry and decreases the relapse rate (Table 9). However, the optimal dose and duration of treatment remain uncertain, and few data exist documenting the efficacy of corticosteroids for patients cared for in outpatient settings. There was a great deal of variability in the dosage, length of treatment, administration, and setting among the studies evaluated.[62–67] In the largest study, the Systemic Corticosteroids in COPD Exacerbations (SCCOPE) trial, 271 patients admitted for acute exacerbations of COPD at one of 25 Veterans Administration hospitals were assigned to receive placebo or 3 days of IV methylprednisolone followed by a course of oral prednisone.[67] For the combined glucocorticoid group, the risk of treatment failure was reduced by 10% (33% vs 23%), and FEV_1 showed an improvement averaging approximately 0.1 L in the first 3 days of treatment. The change in FEV_1 is similar to the magnitude of benefit reported in smaller trials. The SCCOPE trial demonstrated equivalence between an 8-week regimen and a 2-week regimen, the latter consisting of the following: methylprednisolone, 125 mg IV every 6 h (on days 1 to 3); oral prednisone, 60 mg each day (on days 4 to 7); oral prednisone, 40 mg each day (on days 8 to 11); and oral prednisone, 20 mg each day (on days 12 to 15).

Several trials have examined the time course of improvement in FEV_1 during treatment with systemic corticosteroids. The difference in FEV_1 between glucocorticoid-treated and placebo-treated patients in the SCCOPE trial 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 two trials[63,64] that considered short-term outcomes of emergency department treatment, one[64] observed similar improvements in FEV_1 in patients receiving corticosteroids and placebo, and the other[63] demonstrated a significant improvement in FEV_1 over time for patients receiving corticosteroids but did not compare these patients to those receiving placebo. Those trials that measured FEV_1 changes over longer periods of time, in contrast, have shown more conclusive results.

The most common adverse effect associated with systemic corticosteroids for acute exacerbation of COPD was hyperglycemia.[66,67] In the SCCOPE trial, two thirds of the episodes of hyperglycemia requiring treatment occurred in patients who were known to have diabetes mellitus. Nearly all episodes occurred in the first 30 days, and whether hyperglycemia was more frequent or severe in the 8-week or the 2-week course of therapy was not described.[67]

Antibiotics

Based on 11 randomized, placebo-controlled studies of antibiotic treatment, we concluded that antibiotics are beneficial in the treatment of patients with acute exacerbations of COPD (Table 10).[6,68–77] Patients with more severe exacerbations are more likely to experience benefit than those who are less ill. These conclusions are consistent with those of a recent meta-analysis that included many of the trials reviewed herein.[78] It should be noted that many of the studies that do show benefit were performed before the emergence of respiratory pathogens that are resistant to multiple antibiotics.

In their meta-analysis, Saint and colleagues[78] included nine RCTs of antibiotics. These trials used the following variety of outcome measures: PEFR; duration of exacerbation; Pao_2; symptom score; and overall severity score as determined by a physician. Three of nine studies[6,68–75] found a statistically significant benefit for antibiotics, three found a trend favoring antibiotics, and three failed to show any difference from placebo. The most consistently measured end point across studies, improvement in PEFR, was estimated to improve a mean of 10.75 L/min more in patients treated with antibiotics than in patients treated with placebo (95% confidence interval [CI], 4.96 to 16.54).

Three of these studies[6,68,75] analyzed the efficacy of antibiotics within subgroups defined either by evidence of bacterial infection or by severity of illness. One trial[6] found that an *a priori* selection of

Table 10—*Characteristics of RCTs of Antibiotics in Acute Exacerbations of COPD

Study/yr	Patients, No.	Medication: Treatment Group	Medication: Control Group	Mean PEFR at Entry, L/min	Patients With Purulent Sputum, %	Level of Care	Glucocorticoid Use	Results	Validity
Jørgensen et al[71]/1992	268	Amoxicillin	Placebo	295†	33‡	Opt	Prohibited	= Overall clinical assessment = Symptoms (MD) = PEFR	External 2:5 Internal 3:5
Sachs et al[77]/1995	71	Amoxicillin or cotrimoxazole	Placebo	233	27	Opt	Prescribed	+ Symptoms (pt) + PEFR	External 4:5 Internal 4:5
Petersen et al[73]/1967	19	Chloramphenicol	Placebo	214§	74	Inpt	N/S	= PEFR	External 2:5 Internal 5:5
Anthonisen et al[6]/1987	173	Trimethoprim-sulfamethoxazole, amoxicillin, or doxycycline	Placebo	190	60	Opt	Permitted (42% all)	+ Overall clinical assessment‖ + PEFR‖	External 5:5 Internal 4:5
Nicotra et al[72]/1982	40	Tetracycline	Placebo	160	N/S	Inpt	Permitted (75% abx; 65% pbo)	= Symptoms (pt) = Symptoms (MD) = FEV_1, PEFR, FVC	External 4:5 Internal 4:5
Pines et al[74]/1972	259	Tetracycline or chloramphenicol	Placebo	146	100¶	Inpt	N/S	+ Overall clinical assessment‖ + Symptoms (MD)‖ + PEFR	External 3:5 Internal 4:5
Pines et al[76]/1968	30	Penicillin and streptomycin, penicillin alone	Placebo	88	100	Inpt	N/S	+ Overall clinical assessment‖	External 2:5 Internal 5:5
Elmes et al[75]/1965	58	Ampicillin	Placebo	79	78	Inpt	Prohibited	= Overall clinical assessment + PEFR = Length of stay	External 2:5 Internal 5:5
Berry et al[68]/1960	53	Oxytetracycline	Placebo	N/S	60	Opt	N/S	+ Symptoms (MD), pts with *moderate to severe* exacerbations‖	External 2:5 Internal 3:5
Elmes et al[69]/1957	59	Oxytetracycline	Placebo or no treatment	N/S	N/S	Opt	N/S	+ Duration of symptoms + Work days lost	External 2:5 Internal 5:5
Fear and Edwards[70]/1962	62	Oxytetracycline	Placebo	N/S	N/S	Opt	N/S	+ Symptoms (MD) + Duration of symptoms	External 2:5 Internal 5:5

*abx = antibiotics; inpt = inpatient; N/S = not specified; opt = outpatient; pbo = placebo; pt = patient-assessed; MD = physician-assessed; + = benefit for antibiotic-treated patients over placebo-treated patients; = = no reported benefit of antibiotic-treated patients over placebo-treated patients.
†Estimated from.
‡Sputum color: yellow vs none, clear, or white.
§Weighted average of men's median PEFR and women's median PEFR in control group (n = 10); value for active-treatment group could not be similarly estimated.
‖Significance at $p < 0.05$ level.
¶Moderately purulent or purulent.

patients with more severe exacerbations (using the above-mentioned grading system [Table 1]) identified those more likely to benefit from antibiotic treatment. Patients with type 1 exacerbations (severe) experienced a benefit (antibiotic-treated patients, 63%; placebo-treated patients, 43%). The benefit of antibiotic treatment was less apparent in less severe exacerbations (type 1 vs type 2 exacerbations, 70% vs 60%; type 1 vs type 3 exacerbations, 74% vs 70%). Another study[68] demonstrated that physician-assigned severity was correlated with a likelihood of benefit from antibiotics. Among patients with "mild" attacks, there were no significant differences between patients treated with antibiotics and those treated with placebo. Among patients with "moderate" or "severe" attacks, patients treated with antibiotics had significantly fewer severe symptoms on days 2 and 7. A third study[75] demonstrated a similar relationship between the severity of the exacerbation and the benefit from antibiotics. However, this study included patients with clinical evidence of pneumonia among those with severe exacerbations.

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 of antibiotics for this condition. 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.[79]

Oxygen Therapy

Oxygen therapy provides enormous benefits to patients with acute exacerbations of COPD who are hypoxemic (*ie*, the Po_2 level in arterial blood is reduced). Oxygen relieves pulmonary vasoconstriction and right heart strain, and lessens myocardial ischemia, thereby improving cardiac output and oxygen delivery to the CNS and to other critical organs. There is also a substantial amount of evidence supporting 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 the risk 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 (*ie*, oxygenated erythrocytes have lower capacity for CO_2 than deoxygenated erythrocytes).

Based on four Obs studies,[80–83] we concluded that oxygen administration in patients with acute exacerbations of COPD may result in hypercarbia but that there are methods for identifying the patients at highest risk for developing respiratory failure associated with oxygen administration.

A study[80] of 23 patients with respiratory failure accompanying COPD (EV, 3:4; internal validity, Obs 1b) who were given 28% oxygen demonstrated that arterial Pco_2 increased in 17 patients, with a mean rise of 4 mm Hg (range, −2 to 11 mm Hg). The authors stated that in no patient was serious CO_2 retention encountered. A study[83] of seven patients (EV, 3:4; internal validity, Obs 4) with acute exacerbations given both 24.5% and 28% oxygen demonstrated that Pco_2 increased in six of the seven patients. A study[82] of 53 patients (EV, 1:4; internal validity, Obs 2b) with acute exacerbations who were given graded oxygen therapy to raise oxygen saturation had similar findings. All but three patients had elevations in Pco_2, and the greatest rise was observed in patients who presented with the lowest Pao_2 levels. The largest study[81] (EV, 2:4; internal validity, Obs 1b) to address this issue enrolled 50 patients with acute exacerbations of COPD and patients received 24% oxygen, followed by 28% oxygen if hypoxemia persisted. Thirteen of the pa-

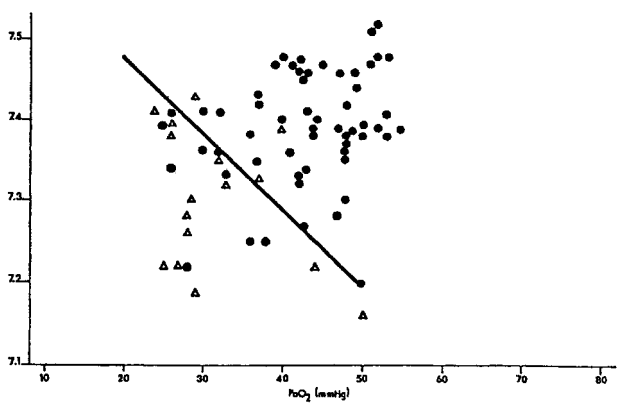

FIGURE 1. The discriminant function, pH = 7.66–0.00919 (Pao_2), helps to identify patients at risk for carbon dioxide retention after the administration of supplemental oxygen. When the patient's observed Pao_2 is entered into the equation, the pH that has been calculated can be compared with the measured pH to distinguish between high-risk 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 represent Pao_2 and pH values on hospital admission of patients who were eventually intubated (triangles) or not nonintubated (circles) in a study evaluating this predictive model. The diagonal line reflects values of the discriminant function and separates high-risk and low-risk patients. Adapted with permission from Wysocki et al.[98]

tients (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, baseline pulmonary function test results, or initial response to therapy. Notably, the relationship between arterial pH and Pa_{O_2} at the time of presentation was predictive of respiratory failure but resting P_{CO_2} was not. The authors derived a discriminant function (Fig 1) for predicting respiratory failure (pH = 7.66 – 0.00910 Pa_{O_2}) that had a sensitivity of 77%. The authors then validated this predictive function in a cohort of 76 subsequent patients, 16 of whom (21%) required mechanical ventilation. Of these 16 patients, 13 had values of pH and Pa_{O_2} that intersected below the discriminant line (sensitivity, 81%). Although, to our knowledge, this predictive model does not currently see heavy use, it does emphasize that patients with simultaneous hypercarbia and hypoxemia are at the greatest risk of developing respiratory failure.

To our knowledge, there are no available data directly addressing the titration of oxygen after an acute exacerbation of COPD. Perhaps the best data can be extrapolated from the Nocturnal Oxygen Therapy Trial, which found that 20% of the 800 patients studied no longer required oxygen 3 weeks after hospital discharge after acute exacerbations of COPD.[84]

Mucus Clearance Strategies

Expectorants, Mucolytics, and Mucokinetics: Based on five RCTs[73,85–88] involving five different drugs, we concluded that pharmacologic mucus clearance strategies have not been demonstrated to shorten the course of treatment for 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 FEV_1 between treatments in any study. Comparisons tested included domiodol vs control (EV, 1:5; internal validity, Exp 1:5),[85] bromhexine vs placebo (EV, 2:5; internal validity, Exp 5:5),[86] ambroxol vs control (EV, 2:5; internal validity, Exp 3:5),[87] S-carboxymethylcysteine vs bromhexine (EV, 3:5; internal validity, Exp 4:5),[88] and potassium iodide vs chloramphenicol, physiotherapy, and placebo (EV, 2:5; internal validity, Exp 1:5).[73] Of the five trials measuring subjective symptom scores on difficulty with expectoration, only two[85,87] reported significant differences ($p < 0.01$) favoring the mucolytic drug over the control.

Physical and Respiratory Therapies: Based on three RCTs[73,89,90] of chest physiotherapy and one Obs study,[91] we conclude that mechanical percussion of the chest as applied by physical/respiratory therapists is ineffective and perhaps even detrimental in the treatment of patients with acute exacerbations of COPD. None of the randomized trials (EV, 3:5, internal validity, Exp 3:5[89]; EV, 2:5; internal validity, Exp 1:5[73]; and EV, 2:5; internal validity, Exp 1:5[90]) reported any improvement in ventilatory function (either FEV_1 or FVC). One RCT[90] described a significantly lower FEV_1 in patients who received chest percussion therapy compared with control subjects. A similar transient decrease in FEV_1 after chest percussion was previously described in an uncontrolled study.[91] No other adverse effects were reported.

Noninvasive Positive-Pressure Ventilation

Based on five RCTs[92–96] and five Obs studies,[99–103] we concluded that noninvasive positive-pressure ventilation (NPPV) is a beneficial support strategy that, in selected hospitalized patients with respiratory failure, decreases the likelihood of requiring invasive mechanical ventilation and, possibly, improves survival time (Table 11). In some of these studies, the exclusion criteria were omitted from the reports, while in others, exclusion criteria included significant cardiovascular disease, lack of mental capacity, presence of pneumonia, and concern about upper airway narrowing or obstruction. As such, the selection criteria for this therapy remain unclear.

Among the four RCTs[92–95] that compared NPPV to a standard therapy control, a significant difference in need for intubation was found in two trials,[94,95] with reduced need for intubation in the NPPV groups (26% vs 74% in a study involving 85 patients[94]; 9% vs 67% in a study involving 23 patients[95]). A fifth trial, comparing NPPV to a respiratory stimulant medication (doxapram) demonstrated a mortality benefit associated with NPPV that was not statistically significant.[96] A meta-analysis[97] published in 1996 that included three of the above trials, as well as three published abstracts[97a,97b,97c] and one other published study,[98] concluded that the risk of death was lower in patients who were randomized to receive NPPV (odds ratio, 0.29; 95% CI, 0.15 to 0.59), as was the risk of requiring invasive mechanical ventilation (odds ratio, 0.20; 95% CI, 0.11 to 0.36). The results from four prospective case series[99–102] were similar to those from the RCTs when NPPV-treated patients were compared to historical control subjects. One Obs study[103] found no increased effectiveness of NPPV over more conventional treatment and observed a large number of adverse effects associated with the use of NPPV.

Additional questions addressed in the literature

Table 11—*Randomized Studies Comparing Patients Receiving NPPV vs Nonventilatory Control Subjects**

Study/yr	Patients, No.		Intervention		Need for Intubation		Mortality		Blood Gas Improvement†			Study Validity	
	NPPV	Control	Type	Duration	NPPV	Control	NPPV	Control	NPPV		Control	External	Internal
Angus et al[96]/1996	9	8	N, PS	4 h once	NR	NR	0	3 (38)	Yes‡	NR	No	3:5	1:5
Barbé et al[92]/1996	10	10	N, BV	3 h, twice/d	0	0	NR	NR	Yes‡	=	Yes‡	3:5	2:5
Bott et al[93]/1993	30	30	N, VC	≤ 16 h/d	0/30 (0)	2/30 (7)	3/30 (10)	9/30 (30)	Yes NR	>	No NR	2:5	2:5
Brochard et al[94]/1995	43	42	FM, PS	≥ 6 h/d	11/43 (26)‡	31/42 (74)	4/43 (9)‡	12/42 (29)	Yes‡	NR	No	2:5	3:5
Kramer et al[95]/1995	11	12	N, BV	≥ 8 h/d	1/11 (9)‡	8/12 (67)	1/16 (6)	2/15 (13)	NR		NR	2:5	2:5

*BV = bilevel ventilation; N = nasal; FM = face mask; PS = pressure support; VC = volume cycled; Yes = within-group improvement pretreatment vs posttreatment; No = no improvement within group; = = no significant difference between groups; > = statistically significant difference in improvement between groups. See Table 9 for other abbreviations not used in text. Values given as No. of persons/No. in group (%), unless otherwise indicated.
†Improvements in blood gas levels were defined differently in different studies. Results reported herein are based on the definitions of each study.
‡Significance at $p < 0.05$ level.

include comparisons between NPPV and invasive ventilation, optimal NPPV delivery methods, and predictors of the successful application of NPPV. Four prospective controlled studies compared types of NPPV delivery methods (EV, 3:5; internal validity, Exp 0:5[104]; EV, 1:5; internal validity, Exp 1:5[105]; EV, 1:5; internal validity, Exp 1:5[106]; and EV, 4:5; internal validity, Exp 2:5[107]). Outcomes of interest were the effect on gas exchange, the need for intubation, mortality, adverse effects/side effects, and the comfort with which the devices may be used. No significant differences in these parameters were seen among the various modes of ventilation. A retrospective study attempting to identify parameters that could predict a successful outcome with the use of NPPV looked at anthropometric and demographic characteristics, nutritional status, spirometry, blood gas levels, and causes of acute exacerbation of COPD. Factors that predicted success included higher pH, lower $PaCO_2$, and higher FVC ($p < 0.05$). Poor outcomes were associated with a diagnosis of pneumonia, poor nutritional status, and decreased compliance with the apparatus.[108,124,125]

Research Priorities

In a disease held responsible for 5% of all deaths in the United States, enormous disability, and $18 billion dollars in annual health-care costs, the paucity of primary data on therapeutics is startling. We found that in more than 40 years of research, fewer than 1,100 patients had been enrolled in randomized, placebo-controlled trials of antibiotics, fewer than 650 patients had been enrolled in studies of corticosteroids vs placebo (before the 1999 SCOPPE trial, the count was less than 400), and virtually no controlled trials (to our knowledge) have enrolled patients with milder (outpatient) 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 symptomatology, quality of life, and interval before subsequent relapse are all important to patients. Given these opportunities, our first research objectives must include untangling the questions surrounding the selection of patients for antibiotic and corticosteroid treatment, identifying optimal dosing

and durations for these agents, and determining to what degree broad-spectrum and narrow-spectrum antibiotics have similar efficacy.

There are a number of potentially promising new research directions as well, including the following: (1) the components of mucus formation, content, release, and transport; (2) strategies for improving muscle strength and reducing muscle fatigue; (3) therapies aimed at aborting the exacerbation cycle, including arrest of the inflammatory cascade; (4) strategies aimed at preventing infectious exacerbations, perhaps through reducing bacterial adherence or limiting cellular damage in the presence of microorganisms; and (5) the determination of biological markers of infection and inflammation (*eg*, antielastase, antioxidant, and cytokine release or action) in the blood and/or sputum.

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