Fondazione IRCCS Policlinico San Matteo Biblioteca Direzione Scientifica

PV116 0382.503.561-497

SBBL - Richiesta Fotocopia Articolo	
Tipo di richiesta (#)	SBBL (36851)
Settimana	16
Titolo rivista	Drugs and Aging
ISSN:	1170-229X
Volume (Fascicolo) Anno : Pagine	24 (4) 2007 : 303-24
Autori	Kunisaki K et all
Titolo articolo	Mangement of Acute Exacerbation of Obstructive Pulmonary Disease in the
Data Richiesta	20/04/2007
Data Validazione	20/04/2007
Provenienza	CATALOGO
Mezzo trasmissione	FAX
Urgenza	normale
Utente Richiedente	
Nominativo	Emanuela Barisione
Qualifica	medico ricercatore
Contatti con l'utente	biblioteca@grg-bs.it
Note Richiedente	se possibile chiedo cortesemente l'articolo in formato pdf
Biblioteca richiedente	
Codice biblioteca:	BS011
Ente:	Biblioteca - Gruppo di Ricerca Geriatrica
Tel:	030-3757538
Fax:	030-48508
Email	biblioteca@grg-bs.it

Firma del referente

In base al DL 16 novembre 1994 n. 685 art.5 e in attuazione della direttiva CEE 92/100, il materiale viene fornito ai fini esclusivi di studio personale e sostituisce la trascrizione manuale. Il richiedente si assume ogni responsabilità per l'uso che ne verrà fatto essendo vietata qualsiasi riproduzione o pubblicazione (L. 159 del 22.05.93)

Firma del richiedente

REVIEW ARTICLE

Drugs Aging 2007; 24 (4): 303-324
1170-229X/07/0004-0303/$44.95/0

© 2007 Adis Data Information BV. All rights reserved.

Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease in the Elderly

An Appraisal of Published Evidence

Ken M. Kunisaki,[1] *Kathryn L. Rice*[1,2] and *Dennis E. Niewoehner*[1,2]

1 University of Minnesota, Minneapolis, Minnesota, USA
2 Minneapolis Veterans Affairs Medical Center, Minneapolis, Minnesota, USA

Contents

Abstract . . . 303
1. Objectives . . . 304
2. Disease Definition and Aetiology . . . 304
3. Burden of Disease . . . 304
4. Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): Definition and Impact . . . 305
5. Aetiology and Pathogenesis of Acute Exacerbations of COPD . . . 306
6. Aging and COPD Exacerbations . . . 307
7. Pharmacological Treatment of Acute Exacerbations of COPD . . . 307
   7.1 Bronchodilators . . . 308
   7.2 Corticosteroids . . . 310
   7.3 Antibacterials . . . 312
8. Other Therapies for Acute Exacerbations of COPD . . . 313
   8.1 Oxygen Therapy . . . 313
   8.2 Non-Invasive Ventilation . . . 314
9. Prevention of Acute Exacerbations of COPD . . . 316
10. Conclusion . . . 318

Abstract

Chronic obstructive pulmonary disease (COPD) is a debilitating disease with rising worldwide prevalence. Exacerbations of COPD cause significant morbidity and become more common with advancing age. Healthcare providers caring for elderly patients should therefore be familiar with effective treatments for exacerbations of COPD. An extensive body of literature has identified several effective drug therapies for exacerbations. These drugs include inhaled bronchodilators, systemic corticosteroids and antibacterials. The two main classes of inhaled bronchodilators are β-adrenoceptor agonists and anticholinergics. These drugs optimise lung function during exacerbations, with neither class demonstrating clear superiority over the other. Systemic corticosteroids are effective when used either for inpatient or outpatient treatment of exacerbations. They hasten recovery from exacerbations and reduce relapse rates. Antibacterials decrease morbidity from exacerbations and may decrease mortality in the more severe exacerbations.

Other effective therapies for the treatment of acute exacerbations of COPD include oxygen and non-invasive ventilation. Oxygen can be safely administered in acute exacerbations associated with hypoxaemia, with titration of oxygen delivery to a goal oxygen saturation of 90%. Non-invasive ventilation reduces the morbidity and mortality associated with acute exacerbations complicated by hypercapnic respiratory failure. Strategies to prevent COPD exacerbations include smoking cessation, long-acting inhaled β-adrenoceptor agonists, inhaled long-acting anticholinergics, inhaled corticosteroids and vaccination. Mucolytic agents, pulmonary rehabilitation, and case management programmes may also reduce exacerbation risk, but the current evidence supporting these interventions is weaker.

1. Objectives

The objectives of this review article are to:
1. Discuss the definition, aetiology, and health impact of acute exacerbations of chronic obstructive pulmonary disease (COPD).
2. Review the published literature on effective treatment of acute exacerbations of COPD.
3. Highlight the available literature pertaining specifically to treatment of elderly persons with acute exacerbations of COPD.
4. Familiarise readers with strategies to prevent acute exacerbations of COPD.

2. Disease Definition and Aetiology

COPD has traditionally encompassed the clinical conditions of chronic bronchitis and emphysema. This classification scheme, however, has many weaknesses. Chronic bronchitis, or the presence of cough and sputum production for at least 3 months in 2 consecutive years, fails to highlight the clinical significance of airflow obstruction in the impact of this disease. Emphysema is a pathological diagnosis, and is one of many other pathological abnormalities found in the lungs of patients with COPD. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has thus defined COPD as "a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gasses."[1]

This definition shifts the focus away from the labels of emphysema and chronic bronchitis, while highlighting the need to demonstrate airflow limitation in order to definitively diagnose COPD. The presence of COPD is thus confirmed by spirometric testing, which shows a reduction in the ratio of the forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC).

For the vast majority of patients afflicted with COPD, the "noxious particles or gasses" mentioned in the GOLD definition come from tobacco smoke. Efforts to reduce tobacco use have been successful in many countries, but worldwide tobacco consumption continues to increase.[2] Exposure to indoor pollution in the form of biomass fuels (for cooking and heating) also increases the risk of developing COPD, particularly in developing countries.[3-5] Other environmental exposures, such as occupational dusts and fumes, also increase the risk of developing COPD.[6]

3. Burden of Disease

COPD is a major global health problem, and despite the advances of modern medicine, the prevalence and mortality of COPD continue to rise. COPD is currently the fourth leading cause of death worldwide and is projected to rise to the third leading cause by 2020.[1] When disability is considered, COPD is projected to rise from the 12th leading cause of worldwide disability in 1990 to the fifth leading cause by 2020.[7] The economic burden of this disease is also substantial. In the US, COPD is

© 2007 Adis Data Information BV. All rights reserved.

responsible for 13.8 million office visits and more than 670 000 hospitalisations annually.[8] Among adults ≥25 years old, COPD was listed as a primary or secondary diagnosis in 8.5% of all US hospitalisations, but among patients ≥65 years old, COPD accounted for 11.3–15.1% of all hospital admissions.[9] The overall direct and indirect medical cost of COPD for the US in 2004 was estimated to be in excess of $US37 billion.[8]

4. Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD): Definition and Impact

The morbidity and economic cost of COPD are driven in large part by episodes of acute worsening of the underlying disease – commonly referred to as acute exacerbations of COPD. The precise definition of an acute exacerbation varies. The most widely referenced criteria are those of Anthonisen and colleagues[10] – acutely worsened dyspnoea, sputum purulence, and/or an increase in sputum volume – though these criteria were designed as part of a clinical trial and not for implementation in patient care settings.

More recently, an international working group proposed defining COPD exacerbations as "a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD."[11] This definition remains clinical in nature, and reflects the current lack of objective criteria for defining exacerbations. In addition to the symptoms included in the criteria of Anthonisen and colleagues,[10] other symptoms associated with acute exacerbations of COPD can include wheezing, cough, fatigue, malaise and worsening exercise tolerance.

Spirometry often demonstrates decreases in FEV_1 and peak expiratory flow. While these changes may predict the outcome of an exacerbation,[12] they can lag behind the clinical symptoms[13] and vary in degree of change; thus spirometry is generally not used in the definition of an acute exacerbation of COPD. To date, there are no biomarkers with adequate sensitivity or specificity for identifying acute exacerbations of COPD, though this remains an area of active research.[14]

The severity of acute exacerbations of COPD can vary widely. At one extreme, patients may experience only a transient, mild increase in dyspnoea; at the other extreme, patients may experience overt respiratory failure requiring hospitalisation and mechanical ventilation. Mild exacerbations may frequently go unreported. Even among participants in longitudinal COPD research cohorts, ≈50% of exacerbations are never reported to the research team.[13,15] In one prospective cohort of 101 patients with moderate-to-severe COPD (mean FEV_1 42% of predicted), the average decrease in lung function at onset of exacerbation was small (≈5% from baseline), reflecting the fact that most exacerbations were defined by symptom changes on diary cards and did not require medical intervention.[13]

As might be expected, changes in lung function are appreciably larger among patients who seek medical attention for exacerbations. Assuming that recovery of lung function approximates premorbid values, patients treated for exacerbations as outpatients appear to have lost ≈20% of their baseline FEV_1 at initial presentation.[16] Patients who require hospitalisation for an exacerbation may lose as much as 30% of their baseline FEV_1 in the short term.[17,18] Therefore, it is not surprising that severe exacerbations requiring medical intervention have a substantial and protracted impact on health status.

Severe exacerbations requiring hospitalisation carry with them a substantial risk of death during the hospitalisation, though estimates vary anywhere from 3% to 30% depending on the particular subgroup studied.[19] The lower mortality estimates largely arise from studies investigating overall in-hospital mortality of all patients admitted for COPD exacerbations,[19,20] while the upper estimates derive from studies investigating mortality of patients specifically admitted with respiratory failure or admitted to the intensive care unit.[21,22] COPD exacerbations requiring hospitalisation also carry a substantial risk of recurrence and death over the ensuing months. In a Canadian administrative database of

© 2007 Adis Data Information BV. All rights reserved.

22 620 patients discharged for COPD exacerbations, 25% required readmission over the next 12 months and 11% died over that period.[23] A smaller, but prospective, single-hospital, Dutch study of 171 patients admitted for COPD exacerbations found that 55% required readmission and 23% died over the subsequent 12 months.[24] Among patients admitted with hypercapnia, the prognosis is even worse: a cohort study of 1016 patients admitted with hypercapnia found that 44% of patients were readmitted within 6 months, and 33% died over that short period.[22]

Less severe exacerbations not requiring hospitalisation are also associated with significant health risks. In particular, a subset of patients with COPD appears to experience frequent, recurrent exacerbations. These patients experience a more rapid decline in quality of life[15,25,26] and may additionally experience a more rapid rate of decline in lung function.[27]

5. Aetiology and Pathogenesis of Acute Exacerbations of COPD

Multiple factors can cause acute exacerbations of COPD, including bacterial infections, viral infections, atypical infections and environmental pollution; however, a substantial portion of exacerbations have no clear aetiology.

Pathogenic bacteria are found in ≈50% of patients with an acute exacerbation of COPD.[28-31] The most common organisms are *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *H. parainfluenzae*. However, the issue of differentiating colonisation from infection has been problematic, with bacteria routinely recovered from sputum samples from patients with stable (non-exacerbated) COPD.[31] At the same time, recent studies have isolated new strains of bacteria[32] and demonstrated strain-specific immune responses during acute exacerbations,[33] findings which suggest that true infection is truly a trigger for many exacerbations.

Studies of viral identification in COPD exacerbations have faced similar issues. When advanced polymerase chain reaction techniques are employed, viruses can be demonstrated in ≈40% of acute exacerbations of COPD, with picornaviruses (of which rhinoviruses are a member) being the most commonly demonstrated.[34,35] However, potentially pathogenic viruses have also been identified in respiratory secretions during stable COPD, so a problem exists in terms of assigning causality.[35] Other viruses found during exacerbations include influenza, parainfluenza, respiratory syncytial virus, adenovirus and human metapneumovirus.

The atypical organisms *Mycoplasma pneumoniae* and *Chlamydia* spp. have been implicated in acute exacerbations of COPD, though their importance is unclear. The available evidence suggests that *Chlamydia* is rarely responsible, being found in only 4–5% of acute exacerbations,[36,37] though it may be more frequently found in the most severely ill. One study of patients mechanically ventilated for respiratory failure showed acute serological evidence of *Chlamydia* in seven of 38 patients (18%), though concomitant bacterial pathogens were present in two of those seven cases.[29] The significance of *Mycoplasma* infection is difficult to assess, with one study demonstrating serological conversion in 14% of acute exacerbations, although in 71% of these cases, there was serological conversion for another respiratory organism as well; when these cases were excluded, *Mycoplasma* as the sole infectious agent was present in only 4% of hospitalisations.[38]

In addition to infections, environmental pollution has been implicated as a cause of acute exacerbations of COPD. Industrialisation of societies leads to increased production of particulate matter <10μm in diameter, sulphur dioxide, nitrogen dioxide and ozone, all of which are pro-inflammatory to the lung mucosa. Particularly with ozone, increases in environmental concentrations lead to increased risk of hospitalisation for COPD.[39] Up to 9% of admissions for acute exacerbations of COPD may be related to atmospheric pollutants, particularly during the summer months.[40]

© 2007 Adis Data Information BV. All rights reserved.

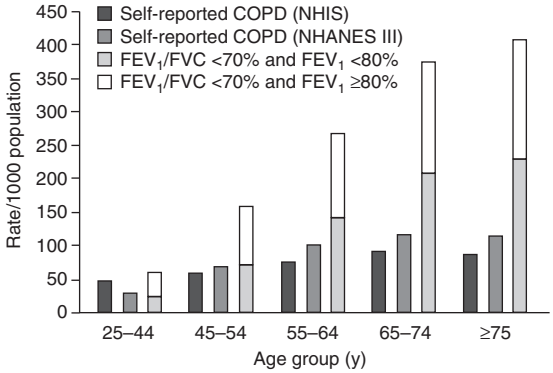

Fig. 1. Estimated prevalence of self-reported chronic obstructive pulmonary disease (COPD) by age group in the US: questionnaire data from the National Health Interview Survey (NHIS) 1988–94,[42] and questionnaire and pulmonary function data from the Third National Health and Nutrition Examination Survey (NHANES III) 1988–94[43] (reproduced from Mannino et al.,[41] with permission). **FEV_1** = forced expiratory volume in 1 second; **FVC** = forced vital capacity.

6. Aging and COPD Exacerbations

The prevalence of COPD, both by self-report and by spirometry, increases with age (figure 1).[41] This increase may be due to (i) the slowly progressive nature of the disease, which often does not manifest itself until later in life; and/or (ii) the fact that COPD is more likely to become symptomatic late in life because of COPD-moderated loss in lung function coupled with normal age-related loss of lung function. Because the prevalence of COPD increases with age, it comes as no surprise that exacerbations also become more prevalent with advancing age. In the US in 2000, of the estimated 726 000 hospitalisations for COPD, 478 000 (66%) occurred in individuals >65 years of age, in whom the hospitalisation rate far exceeded that in younger people (table I).[41]

Several studies have also identified age as an independent risk factor for the development of COPD exacerbations and hospitalisations,[44-46] though others have not.[47-49] In a prospective, large (n = 1829), multicentre clinical trial involving COPD patients, advancing age was found to be a strong independent risk factor for an exacerbation requiring healthcare intervention and an exacerbation requiring hospitalisation.[50] The relative hazard increased by 9% for every 5 years over the age of 40 years for exacerbation and by 36% for every 5 years over the age of 65 with respect to hospitalisation.[50] In patients who have been hospitalised, multiple studies have identified advancing age as an independent risk factor for in-hospital mortality,[21,22,51-53] highlighting the impact of exacerbations in the elderly.

The reasons behind the association between aging and COPD exacerbations are not entirely clear. Age-related decreases in respiratory secretion clearance from small airways may contribute to increased risk of bacterial colonisation and/or infection.[54] Worsened expiratory flow limitation related to both normal aging and COPD may additionally impair clearance of infectious organisms. The increased prevalence of aspiration in the elderly may represent yet another mechanism of increased COPD exacerbation risk.[55] Aging is also associated with declines in both adaptive and innate immunity, and these declines may predispose elderly patients to respiratory infections.[56]

7. Pharmacological Treatment of Acute Exacerbations of COPD

Drugs used to treat acute exacerbations of COPD currently consist of three main established classes of therapy: (i) bronchodilators; (ii) corticosteroids; and (iii) antibacterials. We will review the published evidence supporting the use of these medications (see sections 7.1–7.3). For readers interested in further information, we also recommend the GOLD guidelines[1] and the joint statement from the Ameri-

Table I. Estimated number of annual chronic obstructive pulmonary disease (COPD) exacerbations and annual COPD hospitalisation rate by age (US, 2000)[41]

Age (y)	Estimated number of annual COPD hospitalisations	Estimated annual COPD hospitalisation rate (per 10 000 persons)
25–44	37 000	4.5
45–54	77 000	20.8
55–64	134 000	55.9
65–74	202 000	111.6
≥75	276 000	166.3
Total	**726 000**	**40.8**

© 2007 Adis Data Information BV. All rights reserved.

can Thoracic Society (ATS) and European Respiratory Society (ERS).[57]

7.1 Bronchodilators

Short-acting β_2-adrenoceptor agonists (SABAs) and anticholinergics are the main bronchodilators used to treat acute exacerbations of COPD. β_2-Adrenoceptors are expressed on airway smooth muscle cells, and SABAs (which include salbutamol [albuterol], bitolterol, fenoterol, isoetarine [isoetharine], isoprenaline [isoproterenol], levosalbutamol [levalbuterol], orciprenaline [metaproterenol], pirbuterol, procaterol and terbutaline) increase the concentration of cyclic adenosine monophosphate (cAMP) in these smooth muscle cells; this causes a decrease in intracellular calcium, which results in bronchodilation and improved lung function.[58] Anticholinergics such as ipratropium bromide and oxitropium bromide block muscarinic receptors, and in the airways, inhibition of the muscarinic M_1 and M_3 receptor subtypes reduces smooth muscle contraction.[59] Of note, β-adrenoceptor agonists are available in inhaled, oral and parenteral preparations. Anticholinergics such as atropine are also available in all three forms. However, the available evidence supports the safe and effective use of only the inhaled forms of these drugs, and neither the GOLD[1] nor ATS/ERS[57] guidelines support use of the oral or parenteral forms of these drugs. Our discussion is therefore limited to the inhaled forms of these bronchodilators.

Both inhaled SABAs and inhaled short-acting anticholinergics are thought to be effective in improving FEV_1 during acute exacerbations of COPD, though no placebo-controlled studies have been conducted. Three relatively small randomised trials compared these two classes of bronchodilators. Two studies, one of 39 patients[60] and the other of 52 patients,[61] involving patients admitted for COPD exacerbations compared ipratropium bromide with fenoterol and found no significant differences in FEV_1 between these two classes of bronchodilators. Another study, in 32 patients, compared ipratropium bromide with orciprenaline in patients presenting to emergency departments or pulmonary clinics with acute exacerbations.[62] This study found similar degrees of improvement of FEV_1 and FVC with either bronchodilator. This study also showed a small, but statistically significant, decrease in mean partial pressure of oxygen in arterial blood (PaO_2) [from 64.8mm Hg to 58.6mm Hg] 30 minutes after administration of orciprenaline, but the change was transient, with resolution by 90 minutes following treatment. Patients in the ipratropium bromide arm actually had a small, but statistically significant, increase in their mean PaO_2 (from 68.5mm Hg to 74.5mm Hg) at 30 minutes after ipratropium bromide administration and, as with orciprenaline, this effect was no longer evident 90 minutes following treatment. There appeared to be no clinical consequences of these small, transient gas exchange abnormalities.

While SABAs and anticholinergics appear to have similar physiological effects on lung function improvement, they work through different mechanisms, and there has been long-standing interest in combining the two classes of drugs for additional benefit. In patients with stable (non-exacerbated) COPD, existing data suggest an additive effect from combination therapy,[63,64] but this effect is not seen during acute exacerbations. Five randomised studies comparing a SABA regimen with an anticholinergic plus SABA regimen during acute exacerbations were unable to demonstrate any statistically significant difference in lung function between treatment groups.[61,65-68]

The delivery method of inhaled bronchodilator therapy has also been investigated, as these medications can be delivered via either nebulisation or via metered-dose inhaler. Seven randomised, controlled trials have addressed this question in acute exacerbations of COPD.[69-75] Of these studies, only one small, non-blinded study involving seven COPD patients showed some apparent benefit for nebuliser therapy;[73] the other six studies that addressed the issue of nebuliser versus metered-dose inhaler therapy showed no significant differences between delivery methods in a pooled total of 158 patients.[69-72,74,75]

© 2007 Adis Data Information BV. All rights reserved.

Of note, nearly all these trials used spacer devices with the metered-dose inhalers. Use of spacer devices may additionally be of benefit for elderly patients, who often have cognitive or physical impairments that give rise to difficulties with use of metered-dose inhaler devices that can often be overcome with the use of spacer devices.[76,77]

In one study of 17 young (age 20–36 years) and 17 elderly (age 60–76 years) healthy volunteers, bronchodilator responses to salbutamol were decreased in elderly volunteers compared with their younger counterparts.[78] This suggests that in elderly patients, inhaled β-adrenoceptor agonists may not be as effective as in the young, though it is not clear if these findings can be extrapolated to patients with COPD. Another study suggested that bronchodilator responses to β-adrenoceptor agonists, but not to anticholinergics, decrease with age.[79] However, because this study was largely composed of patients with an asthmatic phenotype, extrapolating these findings to patients with COPD may be inappropriate. There is a lack of studies on the independent effect of age on inhaled bronchodilator responses in the specific setting of COPD.

Adverse effects of inhaled bronchodilators do not appear to be significantly different between the young and the elderly, though comparison studies are largely lacking. One small study of 17 elderly and young patients (mean age 71 and 23 years, respectively) attempted to compare the adverse effects of inhaled bronchodilators in elderly versus young patients.[80] Inhaled β-adrenoceptor agonists increased heart rate, lowered serum potassium and prolonged the cardiac QT interval, but there were no significant differences in the magnitude of these changes between young and elderly patients. Because the study was small, however, it may have been underpowered to detect these differences.

Hypokalaemia, tachycardia and cardiac QT interval prolongation are all adverse effects of concern in the elderly. β-Adrenoceptor agonists frequently cause hypokalaemia and, in fact, high doses of inhaled bronchodilators are effective when used in the treatment of hyperkalaemia.[81] β-Adrenoceptor agonists have also been associated with arrhythmias, particularly atrial fibrillation,[82,83] and are known to commonly cause tachycardia, which may be problematic for the elderly, given their higher prevalence of coronary artery disease. Because elderly patients are often taking other medications that may cause hypokalaemia (such as potassium-wasting diuretics) and QT interval prolongation (such as amiodarone, antibacterials, antidepressants and antipsychotics), clinicians should be aware of these potential adverse effects. Ipratropium bromide does not typically cause electrolyte abnormalities but may increase the risk of supraventricular tachycardia.[84] The main adverse effect of ipratropium bromide is dry mouth,[85,86] but some cases of urinary retention in older men with prostatic hypertrophy have been reported[87] and there have been reports of acute angle-closure glaucoma when ipratropium bromide is nebulised.[88]

Of note, the most commonly used β-adrenoceptor agonist in the US is salbutamol, a 50 : 50 mix of the (R)- and (S)-isomers of the drug. Because the (S)-isomer has weak β_2-adrenoceptor activity and was felt to have potentially detrimental pro-inflammatory effects[89] and more potential for adverse effects, a pure (R)-isomer was developed and is now available as levosalbutamol. Levosalbutamol appears to provide a similar degree of bronchodilation as salbutamol when used in stable COPD patients and in patients with acute exacerbations of asthma.[90,91] Two observational studies found no advantage for levosalbutamol over salbutamol in terms of adverse effects among hospitalised patients with obstructive lung disease.[92,93] A third retrospective, observational study compared levosalbutamol use with salbutamol use 1 year previously and concluded that levosalbutamol shortened hospital length of stay.[94] All studies included patients with respiratory diseases other than COPD. These limited data indicate that a large prospective, randomised trial would be required to confirm any potential clinical benefit of levosalbutamol in the treatment of acute exacerbations of COPD.

Methylxanthines are another class of bronchodilators, of which the most commonly available forms are oral theophylline and intravenous aminophyl-

© 2007 Adis Data Information BV. All rights reserved.

line. These agents inhibit phosphodiesterase activity and increase intracellular cAMP levels, though there may be additional pathways by which methylxanthines act in COPD, such as restoration of corticosteroid-responsiveness through histone deacetylase[95] and improved diaphragm function.[96,97] Four published, randomised, placebo-controlled trials of theophylline for the treatment of acute exacerbations of COPD (sample sizes between 30 to 133 patients), showed no improvement in FEV_1 when aminophylline was added to standard therapy.[98-101] There were no significant differences in clinical endpoints such as relapse rates,[98,100] hospital length of stay[101] or hospitalisation from the emergency department.[98]

Methylxanthines also carry with them a significant risk of serious adverse effects. These are generally related to high serum levels,[102] which are of particular concern in the elderly, whose metabolism of methylxanthines is generally decreased and can vary widely.[103,104] A meta-analysis of four randomised studies of use of methylxanthine for acute exacerbations of COPD found a significantly increased risk of nausea and vomiting in the methylxanthine-treated group.[105] There were also trends toward an increase in tremor and palpitations/arrhythmias, though the studies were not powered to look for adverse effects.

Key conclusions regarding the use of bronchodilators for the treatment of acute exacerbations of COPD are listed in table II.

Table II. Use of bronchodilators for the treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD): key points

Both inhaled SABAs and inhaled short-acting anticholinergics are effective in improving lung function during acute exacerbations of COPD, with neither class of bronchodilator demonstrating superiority over the other
Combining SABAs with anticholinergics appears to have no additional benefit over either class of bronchodilator alone in the treatment of acute exacerbations of COPD
Nebuliser therapy and metered-dose inhaler (with a spacer device) therapy provide equivalent degrees of bronchodilation during acute exacerbations of COPD. Spacer devices may be particularly helpful for elderly patients
Methylxanthines have shown no benefit in the treatment of acute exacerbations of COPD

SABAs = short-acting β_2-adrenoceptor agonists.

7.2 Corticosteroids

Corticosteroids represent another cornerstone in the treatment of acute exacerbations of COPD. This therapy has been established on the basis of multiple randomised, controlled trials. Four randomised trials have investigated the use of intravenous[18,106] and oral[17,18,107] corticosteroids in the treatment of acute exacerbations of COPD requiring hospitalisation. All four trials demonstrated improvement in FEV_1 in the corticosteroid group compared with placebo. Three of these studies measured hospital length of stay, with two studies showing a statistically significant decrease in length of stay of 1.2 days[18] and 2 days[17] in the corticosteroid-treated group. The other study showed a statistically nonsignificant trend towards shorter length of stay in the corticosteroid-treated group (by 2 days).[107] Two studies examined relapse rates or treatment failures following hospital discharge.[17,18] One study showed significantly fewer relapses at 30 and 90 days after admission, but these differences were no longer evident at 6 months.[18] The other study measured relapses within 6 weeks following admission and found no differences between the corticosteroid-treated group and the placebo group.[17]

Two randomised studies evaluated oral corticosteroid use in outpatients with acute exacerbations of COPD who did not require hospitalisation.[108,109] One study of 27 patients showed a more rapid improvement in peak flow and dyspnoea scale scores in those treated with corticosteroids.[108] Perhaps more importantly, significantly fewer treatment failures (defined as the need for open-label prednisone or hospitalisation) occurred in the corticosteroid-treated group. The other study enrolled 147 patients with acute exacerbations of COPD who were treated and discharged from the emergency department.[109] This study confirmed the results of the earlier study, with the prednisone-treated group experiencing improved FEV_1, improved dyspnoea scale scores 10 days after treatment and fewer relapses (defined as an unscheduled visit to a physician's office or emergency department within 30 days).

© 2007 Adis Data Information BV. All rights reserved.

Thus, systemic corticosteroids have been shown to improve the course of acute exacerbations of COPD (in terms of spirometric improvement, decreased length of hospital stay and decreased risk of relapse), but questions remain about the dosage and duration of therapy. Dosages have ranged from as low as oral prednisone 30mg once daily[17] to as high as intravenous methylprednisolone 125mg every 6 hours.[18] Data from the largest trial of patients admitted for COPD exacerbations showed no difference between a 2-week course of corticosteroids and an 8-week course, thus suggesting that 2 weeks of therapy is adequate.[18] A study of 36 patients hospitalised for COPD exacerbations compared a 10-day course of corticosteroids with a 3-day course and demonstrated better improvements at 10 days in the 10-day group compared with the 3-day group.[110] Compared with results in the 3-day treatment group, the 10-day corticosteroid treatment group exhibited statistically significant improvements at 10 days in mean FEV_1 (236 vs 68mL, respectively), mean FVC (319 vs 17mL, respectively), and mean PaO_2 (21.2 vs 11.3mm Hg, respectively). The study was underpowered to detect differences in clinical outcomes between the groups.

The adverse effects of systemic corticosteroids are numerous. While the long-term, detrimental adverse effects of chronic systemic corticosteroid therapy (such as osteoporosis, adrenal insufficiency, cataracts and skin thinning) are well-established, the risks of short-term use of systemic corticosteroids for acute exacerbations of COPD are less clear. The most common adverse effect noted in clinical trials of systemic corticosteroids for COPD exacerbations has been hyperglycaemia, with all four inpatient studies of corticosteroids showing more episodes of hyperglycaemia,[18,107] glucosuria[17] or higher mean glucose levels[106] in the corticosteroid-treated groups compared with the placebo groups.

Psychiatric adverse effects from short-term systemic corticosteroids may include insomnia, anxiety and depression. These adverse effects may be dose-related,[111] though in the study using the largest doses of corticosteroids (methylprednisolone 125mg intravenously every 6 hours), there were no significant differences between the corticosteroid-treated and placebo groups in acute psychiatric illnesses requiring psychiatric consultation.[18] The study was not designed or powered to detect less severe psychiatric adverse effects, so these potentially important clinical events may have been missed. An outpatient trial (in which patients received prednisone 40mg once daily) reported significantly more insomnia in the 74 corticosteroid-treated patients compared with the 73 placebo-treated patients (48% vs 21%, respectively; $p = 0.001$) and non-significant trends towards more depression (19% vs 10%, respectively; $p = 0.14$) and anxiety (27% vs 19%, respectively; $p = 0.28$) in corticosteroid-treated patients.[109]

Secondary infections are also of concern when using systemic corticosteroids to treat acute exacerbations of COPD. When systemic corticosteroids were administered for 8 weeks (using a tapering schedule) following admission for a COPD exacerbation, there was a trend towards more re-hospitalisations for serious infections in that group compared with groups receiving either only 2 weeks of corticosteroids or placebo.[18] Systematic reviews of clinical trials not involving COPD patients suggest that brief courses of systemic corticosteroids do confer a small risk of both lethal and nonlethal secondary infections.[112,113] The same may be true for COPD patients who receive short-term systemic corticosteroids, though the available information is inadequate to allow a firm conclusion.

Acute, corticosteroid-induced myopathy has also been associated with use of systemic corticosteroids for acute exacerbations of COPD. Typically, the risk of myopathy increases with increases in corticosteroid dosage[114] and is more commonly found in intubated, critically ill patients,[115] though isolated cases have been reported even following a single oral dose.[116] It is important to be aware of this complication because the myopathy can progress to a severe and chronic myopathy if corticosteroids are not promptly withdrawn.[117]

Gastrointestinal bleeding is still frequently cited as a complication of systemic corticosteroid use. A systematic review on this subject, however, failed to

© 2007 Adis Data Information BV. All rights reserved.

find any such risk;[113] earlier studies suggesting such a relationship had not adjusted for concomitant use of NSAIDs. The only large study that assessed this risk in patients being treated for acute exacerbations of COPD failed to find any increase in the incidence of corticosteroid-related gastrointestinal bleeding.[18]

Key conclusions regarding the use of corticosteroids for the treatment of acute exacerbations of COPD are listed in table III.

7.3 Antibacterials

As discussed in section 5, the most common aetiology for acute exacerbations of COPD is infection, with recovery of bacterial pathogens (and new strains of pathogens) from the lower airways at times of exacerbations occurring frequently. Antibacterials, therefore, might be expected to hasten recovery in these patients. However, antibacterials would not be expected to help exacerbations triggered by viral infections or environmental pollution. Unfortunately, differentiating bacterial exacerbations from non-bacterial exacerbations is clinically quite difficult, short of performing bronchoscopy for lower airway culture collection, a procedure that risks precipitating respiratory failure in those with marginal lung function. Currently, there is no non-invasive test with established ability to discriminate bacterial from non-bacterial COPD exacerbations. Thus, most patients experiencing more severe exacerbations of COPD are empirically treated with antibacterials.

Table III. Use of systemic corticosteroids for the treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD): key points

Systemic corticosteroids hasten the recovery from acute exacerbations of COPD, both for inpatients and outpatients
Systemic corticosteroids reduce the risk of a relapse of an acute exacerbation of COPD, both for inpatients and outpatients
The duration of systemic corticosteroid therapy should not exceed 2 weeks
The optimal corticosteroid dose is not clear, but a starting dose of 40mg of oral prednisone daily (or its equivalent) is reasonable
Clinicians should be aware of the adverse effects of corticosteroid therapy, which include hyperglycaemia, psychiatric adverse effects and weakness suggestive of myopathy

Eleven randomised, placebo-controlled trials have been conducted to determine whether or not antibacterials are effective therapy in the treatment of acute exacerbations of COPD.[10,118-127] A recent meta-analysis concluded that, compared with placebo, antibacterials reduce the relative risk (RR) of death by 77% in patients with moderate to severe exacerbations.[128] This meta-analysis concluded that eight patients would require treatment with antibacterials to prevent one death (95% CI 6, 17). Of note, data from only four of these 11 trials were included in the mortality analysis, which was largely influenced by one particular study conducted in the intensive care unit.[124] In this study of 93 patients with the most severe exacerbations requiring mechanical ventilation, 9% of the antibacterial-treated patients died in the hospital, compared with 39% of the placebo-treated group. When this study was excluded from the mortality analysis, the authors stated that the point estimate of the reduction in risk did not change, but the 95% CIs for the risk reduction and number needed to treat widened and the risk reduction estimate became statistically insignificant. The meta-analysis[128] also suffers the same pitfalls of any meta-analysis: differing definitions of exacerbations, differing inclusion/exclusion criteria, differing treatment regimens (particularly problematic with the wide variety of antibacterials available internationally), differing outcome measures, and the possibility of publication bias against 'negative studies' that were unable to show differences.

The meta-analysis[128] was also unable to draw conclusions on the relationship between severity of illness and effectiveness of antibacterial therapy because of the small number of available studies and incomplete data on severity of illness in the studies. This question has arisen as a result of findings from one of the landmark studies on antibacterials in COPD exacerbations.[10] In that study, exacerbation severity was graded *a priori* according to the presence of three cardinal symptoms of COPD exacerbations: worsening dyspnoea, increasing sputum purulence and/or increasing sputum volume. The presence of all three symptoms was graded as the most

© 2007 Adis Data Information BV. All rights reserved.

severe exacerbation, while the presence of only one of the three symptoms was graded as the least severe. When all three symptoms were present, antibacterials provided the greatest benefit, with 63% of those receiving antibacterials improving compared with 43% of those receiving placebo. In patients with less than three cardinal symptoms, antibacterials were less effective (70% improving vs 60% receiving placebo in those with two cardinal symptoms and 74% vs 70%, respectively, in those with only one cardinal symptom). A separate study also demonstrated that in the absence of purulent sputum (as assessed by comparing sputum sample colour to a colour chart), 32 of 34 patients (94%) spontaneously recovered without antibacterial therapy; the two patients that eventually required antibacterial therapy actually developed purulent sputum prior to receiving the antibacterials.[129] Lastly, the previously discussed study of patients mechanically ventilated for exacerbations of COPD showed significant reductions in mortality when antibacterials were compared with placebo.[124] Thus, the available evidence supports the notion that patients with more severe exacerbations derive the most benefit from antibacterials.

The optimal choice of antibacterial and duration of therapy remain unresolved, as different trials have used differing antibacterial regimens and different durations of therapy. When antibacterials are used, selection of therapy should generally be directed to cover suspected organisms, including *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*, which are the most frequently recovered organisms (see section 5). In the era of antibacterial-resistant organisms, the choice of a specific antimicrobial should also be guided by regional antimicrobial susceptibility patterns. Lastly, for the most severe exacerbations requiring mechanical ventilation, consideration should also be given to coverage of Gram-negative enteric bacteria, such as *Pseudomonas* spp. and *Stenotrophomonas* spp., on the basis of two studies which demonstrated recovery of these organisms in 16%[28] to 28%[29] of patients mechanically ventilated for acute exacerbations of COPD.

Table IV. Use of antibacterials for the treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD): key points

Antibacterials are effective in decreasing morbidity from acute exacerbations of COPD, and may decrease mortality in the more severe exacerbations
Antibacterials are most likely to benefit patients presenting with more severe exacerbations, particularly if sputum purulence is present
The optimal choice of antibacterial agent and duration of therapy are not established

Key conclusions regarding the use of antibacterials for the treatment of acute exacerbations of COPD are listed in table IV.

8. Other Therapies for Acute Exacerbations of COPD

In addition to pharmacological therapy, two other therapies are widely used in the treatment of acute exacerbations of COPD: oxygen therapy and assisted ventilation (see sections 8.1–8.2).

8.1 Oxygen Therapy

Acute exacerbations of COPD are frequently associated with gas exchange abnormalities and patients often present with hypoxaemia with or without hypercarbia. The aetiology of these gas exchange abnormalities is likely multifactorial, with demonstrated elements of both ventilation-perfusion mismatching (possibly from bronchoconstriction and mucus plugging of airways) and increased oxygen consumption (presumably from increased work of the respiratory muscles).[130] Because significant hypoxaemia can lead to metabolic acidosis and end-organ damage, oxygen therapy is routinely administered during acute exacerbations of COPD with associated hypoxaemia. While oxygen therapy reduces mortality in stable (non-exacerbated) COPD patients with resting hypoxaemia,[131,132] the mortality benefits of oxygen therapy in acute exacerbations have not been studied, for reasonable ethical concerns about not treating hypoxaemia in the acutely ill patient.

The main concern of clinicians administering oxygen therapy has been the risk of inducing hypercapnia which could precipitate the need for mechan-

© 2007 Adis Data Information BV. All rights reserved.

ical ventilation. The mechanism of this hypercarbia is not clear, with proposed mechanisms including hyperoxia-induced changes in dead space and hyperoxia-induced release of hypoxic ventilatory drive. Regardless of the mechanism, hypercapnia is a well described phenomenon, particularly when COPD patients inhale very high oxygen concentrations.[133-136] Clinicians have thus traditionally avoided high oxygen concentrations and aimed for the lowest oxygen concentration that provides oxygen saturations of 90% (thus approximating a PaO_2 of 60mm Hg, which is generally adequate for tissue oxygenation). This strategy is often referred to as 'controlled oxygen therapy', implying close monitoring to determine the minimum amount of oxygen required. When a strategy of controlled oxygen delivery is adopted, the risk of hypercapnia appears to be quite low,[137-140] although large, randomised trials in this area are lacking.

Oxygen may also be delivered by a myriad of different systems, though systems that can potentially deliver unwanted high fractions of inspired oxygen (FiO_2), such as face masks with oxygen reservoirs or nasal cannulas with oxygen reservoirs, are generally avoided. The most commonly employed oxygen delivery systems for exacerbations of COPD are nasal cannulas and Venturi masks. Nasal cannulas are less bulky than face masks (and therefore well tolerated by patients), but FiO_2 cannot be adjusted accurately and unintended delivery of high FiO_2 may cause hypercarbia during acute exacerbations of COPD. Venturi masks, in contrast, can more accurately control FiO_2 by using the Bernoulli effect to control the amount of room air entrained into the system, thereby preventing unintended delivery of high FiO_2. However, one small, crossover study of 18 patients demonstrated no difference in the risk of hypercarbia when nasal cannula oxygen was compared with Venturi mask oxygen.[138] The Venturi mask did provide significantly less time with saturations <90% over a 24-hour period compared with nasal cannulas (3.7 vs 5.4 hours over a 24-hour period). Larger studies in this area have not been performed.

The question of how to titrate oxygen therapy following an acute exacerbation of COPD remains largely unstudied. Though some patients with advanced COPD require continuous chronic home oxygen therapy, many patients experience hypoxaemia only during acute exacerbations of COPD and do not require long-term oxygen therapy. This was exemplified in one of the seminal studies of oxygen therapy for stable COPD, the Nocturnal Oxygen Therapy Trial.[131] Although this trial was not specific to patients following an acute exacerbation, of 1043 hypoxaemic COPD patients screened for study entry, between 170 and 201 (16–19%, specific data not reported) resolved their hypoxaemia within a 3-week observation period, such that they became ineligible for the trial.

Key conclusions regarding the use of oxygen for the treatment of acute exacerbations of COPD are listed in table V.

8.2 Non-Invasive Ventilation

In some cases of acute exacerbations of COPD, despite the use of bronchodilators, corticosteroids, antibacterials and controlled oxygen therapy, patients can fail to improve and may progress to overt hypercapnic respiratory failure (generally defined as an arterial partial pressure of carbon dioxide [$PaCO_2$] >45mm Hg). One mechanism of hypercapnic respiratory failure is use of excessive

Table V. Use of oxygen for the treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD): key points

Despite its widespread use, few data are available to guide the optimal use of oxygen for acute exacerbations of COPD
Acute exacerbations of COPD associated with hypoxaemia can generally be safely treated with supplemental oxygen, with titration of oxygen therapy to a goal oxygen saturation of ≈90%, or a PaO_2 of 60mm Hg
Patients should be closely monitored for the development of hypercarbia and the need for ventilatory support if they are being treated with oxygen. If clinical concern for hypercarbia exists (such as the presence of somnolence or mental status changes), arterial blood gas analysis should be performed
If oxygen therapy is newly begun at the onset of an acute exacerbation of COPD, patients should be re-evaluated in the near future to evaluate the need (or lack thereof) for long-term oxygen therapy

PaO_2 = partial pressure of oxygen in arterial blood.

© 2007 Adis Data Information BV. All rights reserved.

amounts of oxygen, as described in section 8.1. More commonly, however, patients are believed to develop a mechanical disadvantage of their diaphragm from the acutely worsened air trapping and hyperinflation. This is thought to lead to worsening hypercapnia and acidosis, thus further impairing optimal muscle metabolism, and thence to a downward spiral culminating in overt ventilatory failure. Historically, patients with hypercapnic respiratory failure from an acute exacerbation of COPD were treated with tracheal intubation and mechanical ventilation in the intensive care unit. However, intubation and mechanical ventilation can lead to multiple complications such as ventilator-associated pneumonia, barotrauma and delirium, which is especially common in the elderly.[141,142] Thus, use of non-invasive ventilation (NIV) for acute exacerbations of COPD complicated by hypercapnic respiratory failure became of interest.

NIV for acute exacerbations of COPD generally entails use of a device capable of delivering inspiratory-phase positive pressure (with or without expiratory-phase positive pressure) via a tight-fitting full-face mask or nasal mask. By pressurising the airway during an inspiratory manoeuvre, NIV reduces the work of breathing and may be beneficial in hypercapnic acute exacerbations of COPD by reducing the energy expenditure of the diaphragm (thus reducing its carbon dioxide production) and/or increasing ventilation to underventilated alveolar units. NIV also allows patients to use the mask intermittently, and thus communicate, swallow medications, eat and drink, which are distinct advantages compared with tracheal intubation.

Multiple studies have now investigated the use of NIV in acute exacerbations of COPD. Indeed, 14 randomised controlled trials investigating the use of NIV in hypercapnic respiratory failure (defined as a $PaCO_2$ >45mm Hg) associated with acute exacerbations of COPD were analysed in a recent systematic review.[143] The review included six studies conducted in intensive care units,[144-149] seven studies conducted in general medical wards[150-156] and one study with an unspecified setting.[157] Two of the included studies were published only in abstract form.[148,157] This systematic review demonstrated reductions in multiple clinically important endpoints when NIV was added to usual medical care. These included reductions in mortality (RR 0.52; 95% CI 0.35, 0.76), risk of treatment failure (RR 0.48; 95% CI 0.37, 0.63), risk of intubation (RR 0.41; 95% CI 0.33, 0.53) and hospital length of stay (weighted mean difference of 3.2 days; 95% CI 2.1, 4.4). The analysis concluded that ten patients would have to be treated with NIV to prevent one death, five patients would have to be treated to prevent one treatment failure (defined as a death, need for intubation or intolerance to treatment) and four patients would have to be treated to prevent one intubation.

Despite the robust body of evidence supporting the use of NIV for hypercapnic acute exacerbations of COPD, some patients ultimately fail NIV and go on to require tracheal intubation and mechanical ventilation. The risk factors for predicting NIV failure have varied in multiple studies, and include high severity-of-illness scores,[158,159] inability to form a good seal with the device,[159] concomitant pneumonia[160] and even low serum albumin levels.[158] There is, however, no widely adapted model for predicting the success or failure of NIV. Thus, when using NIV to treat hypercapnic respiratory failure caused by acute exacerbations of COPD, patients require close clinical monitoring to ensure that they are not amongst the subset of patients for whom NIV will ultimately fail to improve their gas exchange abnormalities. Suggested protocols detailing methods for initiating NIV and monitoring response to therapy have been published,[161] and are beyond the scope of this review. Additionally, there are patients who present with acute indications for urgent intubation (such as haemodynamic instability, respiratory arrest, life-threatening hypoxaemia, or inability to maintain airway protection) for whom NIV should not be used in place of tracheal intubation.

Some clinicians may hesitate to offer tracheal intubation and mechanical ventilation to elderly patients with severe acute exacerbations of COPD because of concerns that such action will carry with it a high risk of death and/or prolonged mechanical ventilation. The mortality of patients requiring inva-

© 2007 Adis Data Information BV. All rights reserved.

sive mechanical ventilation for acute exacerbations of COPD, as mentioned in section 4, can be as high as 30%. However, when studies have examined mortality in acute respiratory failure, diagnosis of COPD has not emerged as an independent risk factor for mortality.[162] In fact, when compared with other diseases for which mechanical ventilation is commonly instituted (such as acute respiratory distress syndrome), mechanical ventilation for COPD is actually associated with a lower risk of mortality, shorter duration of mechanical ventilation and shorter intensive care unit length of stay.[163] However, of relevance to this review, advancing age has been identified as an independent predictor of mortality from any cause of acute respiratory failure.[162,163] The data thus suggest that while many factors may influence the decision of whether or not to institute mechanical ventilation (such as other co-morbidities, previous quality of life and perhaps advancing age), mechanical ventilation for acute exacerbations of COPD carries similar (and perhaps better) prognosis than mechanical ventilation for many other diseases resulting in acute respiratory failure.

Key conclusions regarding the use of NIV for the treatment of acute exacerbations of COPD are listed in table VI.

9. Prevention of Acute Exacerbations of COPD

A discussion of the treatment of acute exacerbations of COPD is incomplete without some discussion of strategies to prevent exacerbations. A full discussion of strategies to prevent exacerbations, however, requires reviewing a rather extensive body of literature and also requires discussion of statistical controversies related to analysis of exacerbation rates,[164] thus placing this type of discussion beyond the scope of this review. Readers interested in a more in-depth analysis of strategies to prevent COPD exacerbations are referred to recent reviews of this topic.[165-167]

Table VI. Use of non-invasive ventilation (NIV) for the treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD): key points

When added to usual medical care for respiratory failure associated with acute exacerbations of COPD, NIV reduces the morbidity and mortality associated with these exacerbations
Because NIV does not eliminate the possible need for tracheal intubation and mechanical ventilation, patients should be closely monitored for response (or lack thereof) to NIV therapy

Cessation of smoking is of paramount importance in the management of all persons with COPD. Smoking cessation slows the rate of decline in FEV_1,[168-170] reduces the risk of COPD hospitalisation[171] and, most importantly, reduces mortality in patients with COPD.[172] Elderly smokers may be less likely to receive smoking cessation advice,[173] but this is not justified by the literature – smoking cessation interventions shown to be effective in the general population (such as counselling, self-help programmes and nicotine replacement) are equally effective in helping elderly persons to quit smoking.[174] Detailed reviews of effective smoking cessation interventions are available elsewhere.[174-176]

In addition to the SABAs discussed in section 7.1, long-acting β_2-adrenoceptor agonists (such as salmeterol and formoterol) have become available, and this class of bronchodilators appears to have some effect in preventing exacerbations of COPD. A recent systematic review[177] concluded that, on the basis of results from four studies comparing salmeterol with placebo,[178-181] salmeterol prevents COPD exacerbations, with 24 patients requiring treatment with salmeterol to prevent one exacerbation (95% CI 14, 98).

Long-acting anticholinergics are also available, of which the only currently approved agent is tiotropium bromide. Tiotropium bromide has also been evaluated in a recent systematic review,[182] and based on the results of eight randomised controlled trials,[183-190] tiotropium bromide also appears to prevent COPD exacerbations, with 14 patients requiring treatment to prevent one COPD exacerbation (95% CI 11, 22).

While use of systemic corticosteroids for acute exacerbations of COPD has been rooted in solid evidence, the role of inhaled corticosteroids is much more contentious. Even among leading authorities in the field of COPD, there is considerable disagreement of opinion on the use of inhaled corticosteroids for COPD.[191,192] Nevertheless, three systematic re-

© 2007 Adis Data Information BV. All rights reserved.

views examining the effect of inhaled corticosteroids on COPD exacerbations have been completed.[166,193,194] Each review used slightly different selection criteria and therefore included a variable number of studies (six[166,193] to ten[194]) when assessing exacerbations, with four studies[195-198] being common to all three reviews. Despite including different studies, each analysis concluded that inhaled corticosteroids reduce the risk of exacerbations, with similar estimates for risk reduction, that is, 24%,[166] 30%[193] and 33%.[194] Only one of these analyses reported a number needed to treat,[194] and this was derived from an analysis of patients with moderate to severe COPD only. The authors concluded that 12 patients would need to be treated with inhaled corticosteroids for 17.7 months to prevent one exacerbation (95% CI 9, 18).

Because of the largely infectious nature of exacerbations, vaccination against respiratory pathogens might be expected to help prevent COPD exacerbations. The two main respiratory pathogens for which adult vaccination is widely available are *S. pneumoniae* (pneumococcus) and influenza virus. Pneumococcal vaccination has not been well studied in patients with COPD; only a few small, underpowered studies[199,200] and retrospective studies that included other lung diseases[201] comprise the bulk of the available data. One recent prospective study in COPD patients interestingly demonstrated a reduction in community-acquired pneumonia (data on exacerbations were not collected) only in those COPD patients <65 years of age, with no reduction in patients ≥65 years of age.[202] The US Advisory Committee on Immunization Practices recommends pneumococcal vaccination for all adults ≥65 years of age, whether or not they have COPD or other comorbidities.[203]

Influenza vaccination has likewise been understudied in COPD, with the available database again consisting of small, randomised, controlled trials[204,205] and large, retrospective studies that included other lung diseases.[206] However, a systematic review on the subject concluded that influenza vaccination was effective in prevention of exacerbations.[207] Importantly, influenza vaccination of patients with COPD also appears to be safe, with no worsening of dyspnoea, exercise capacity or lung function following vaccination.[208,209]

Mucolytic agents (such as acetylcysteine [N-acetylcysteine], carboxymethylcysteine [S-carboxymethylcysteine] and bromhexine) have been evaluated for prevention of COPD exacerbations, the hypothesis being that improved mucus clearance will reduce the risk of exacerbations. A systematic review of the literature that analysed 26 trials involving 7335 patients concluded that use of mucolytic agents results in a very small reduction in the risk of exacerbations.[210] However, there was significant heterogeneity between included studies and the most recent and most carefully designed randomised trial found no reduction in exacerbation risk.[211] In that trial, patients not taking an inhaled corticosteroid did experience a reduction in risk with acetylcysteine, but as this was a subgroup analysis, this result must be interpreted with caution.

Pulmonary rehabilitation has been extensively studied recently, but its effect on modulating exacerbations has not been investigated in depth, with most studies focusing on health status scales and exercise performance. One observational study of 26 patients with COPD suggested that pulmonary rehabilitation reduces exacerbations, when comparing exacerbation frequency before and after pulmonary rehabilitation.[212] A prospective, randomised trial in 200 patients showed that participation in a 6-week pulmonary rehabilitation programme did not reduce the risk of hospital admission, but those in the pulmonary rehabilitation arm, when admitted, had shorter hospital stays.[213] Likewise, a prospective, randomised study of 60 patients showed no reduction in hospitalisations after pulmonary rehabilitation, but the study did find a reduction in the number of exacerbations per patient.[214] The frequency with which pulmonary rehabilitation programmes should be completed to maintain these potential benefits is unclear. One study demonstrated that reductions in exacerbations over 2 years were maintained only in the group of patients who performed pulmonary rehabilitation 1 year after their first pulmonary rehabilitation programme.[215] The mechanisms by

© 2007 Adis Data Information BV. All rights reserved.

which pulmonary rehabilitation might reduce COPD exacerbations are unclear.

Lastly, there has been increasing interest in the use of self-management or case-management programmes to reduce the risk of COPD exacerbations requiring hospitalisation. These programmes may involve many different interventions such as disease education, medication education, 'action plans' such as those used for asthma patients, or regular phone calls from a nurse or respiratory therapist. A recent systematic review was unable to discern any beneficial effect of these interventions, but the authors found the data "too sparse to discern any clinically relevant benefit or harm arising from such interventions".[216] Two studies in particular have demonstrated efficacy in reducing hospitalisations,[217,218] but larger studies will be required before these programmes can be widely and definitively endorsed.

Key conclusions regarding strategies to prevent acute exacerbations of COPD are listed in table VII.

10. Conclusion

COPD increases in prevalence with advancing age and is associated with significant morbidity, mortality and healthcare costs. Acute exacerbations of COPD are particularly problematic for patients with this disease and can be very severe, even culminating in death. Studies investigating the appropriate management of acute exacerbations of COPD have provided good evidence for the beneficial use of bronchodilators, corticosteroids, antibacterials, oxygen and assisted ventilation in the acute phase of the disease. Established strategies to prevent exacerbations of COPD include smoking cessation, pharmacotherapy and immunisations. We found limited data on the independent effects of aging on COPD exacerbation treatment and prevention. Given predictions of worldwide increases in COPD prevalence, this is an area of research demanding further investigation.

Table VII. Strategies to prevent acute exacerbations of chronic obstructive pulmonary disease (COPD): key points

COPD patients at risk should be assessed for implementation of therapy that may help reduce the risk of a future exacerbation
Consideration should be given to use of long-acting β_2-adrenoceptor agonists, long-acting anticholinergics and inhaled corticosteroids
While pneumococcal and influenza vaccinations are not entirely proven to prevent COPD exacerbations, both are safe and should be routinely administered to patients with COPD

Acknowledgements

No sources of funding were used to assist in the preparation of this review.

Dr Kunisaki has received grants from GlaxoSmithKline. Dr Rice has received Speakers' Bureau honoraria from Boehringer-Ingelheim and research grants from Boehringer-Ingelheim and AstraZeneca. Dr Niewoehner has acted as a consultant to Boehringer-Ingelheim, AstraZeneca, sanofi aventis, and Adams Respiratory Therapeutics; has received honoraria from Boehringer-Ingelheim and Pfizer; and has received grants from Boehringer-Ingelheim and GlaxoSmithKline.

References

1. Global Initiative for Chronic Obstructive Lung Disease. Workshop report: global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, updated November 2006 [online]. Available from URL: http://www.goldcopd.com [Accessed 2007 Mar 12]
2. Mackay J, Eriksen M. The tobacco atlas. Geneva: World Health Organization, 2002
3. Sezer H, Akkurt I, Guler N, et al. A case-control study on the effect of exposure to different substances on the development of COPD. Ann Epidemiol 2006; 16: 59-62
4. Ekici A, Ekici M, Kurtipek E, et al. Obstructive airway diseases in women exposed to biomass smoke. Environ Res 2005; 99: 93-8
5. Kiraz K, Kart L, Demir R, et al. Chronic pulmonary disease in rural women exposed to biomass fumes. Clin Invest Med 2003; 26: 243-8
6. Bakke S, Baste V, Hanoa R, et al. Prevalence of obstructive lung disease in a general population: relation to occupational title and exposure to some airborne agents. Thorax 1991; 46: 863-70
7. Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. Lancet 1997; 349: 1498-504
8. National Heart, Lung, and Blood Institute. Morbidity and mortality: 2002 chartbook on cardiovascular, lung, and blood diseases. Bethesda (MD): US Department of Health and Human Services, NIH, NHLBI, 2004 May [online]. Available from URL: http://www.nhlbi.nih.gov/resources/docs/04_chtbk.pdf [Accessed 2007 Feb 27]
9. Holguin F, Folch E, Redd SC, et al. Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. Chest 2005; 128: 2005-11
10. Anthonisen NR, Manfreda J, Warren CP, et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987; 106: 196–204
11. Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. Chest 2000; 117 (5 Suppl. 2): 398S-401S

© 2007 Adis Data Information BV. All rights reserved.

12. Niewoehner DE, Collins D, Erbland ML. Relation of FEV1 to clinical outcomes during exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000; 161: 1201-5
13. Seemungal TA, Donaldson GC, Bhowmik A, et al. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000; 161: 1608-13
14. Hurst JR, Donaldson GC, Perera WR, et al. Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006; 174: 867-74
15. Miravitlles M, Ferrer M, Pont A, et al. Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study. Thorax 2004; 59: 387-95
16. Parker CM, Voduc N, Aaron SD, et al. Physiological changes during symptom recovery from moderate exacerbations of COPD. Eur Respir J 2005; 26: 420-8
17. Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Lancet 1999; 354: 456-60
18. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. N Engl J Med 1999; 340: 1941-7
19. Patil SP, Krishnan JA, Lechtzin N, et al. In-hospital mortality following acute exacerbations of chronic obstructive pulmonary disease. Arch Intern Med 2003; 163: 1180-6
20. Cydullka RK, McFadden ER Jr, Emerman CL, et al. Patterns of hospitalization in elderly patients with asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1997; 156: 1807-12
21. Seneff MG, Wagner DP, Wagner RP, et al. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. JAMA 1995; 274: 1852-7
22. Connors AF Jr, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease: the SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med 1996; 154: 959-67
23. Sin DD, Tu JV. Inhaled corticosteroids and the risk of mortality and readmission in elderly patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001; 164: 580-4
24. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. Chest 2003; 124: 459-67
25. Spencer S, Jones PW, GLOBE Study Group. Time course of recovery of health status following an infective exacerbation of chronic bronchitis. Thorax 2003; 58: 589-93
26. Spencer S, Calverley PM, Burge PS, et al. Impact of preventing exacerbations on deterioration of health status in COPD. Eur Respir J 2004; 23: 698-702
27. Donaldson GC, Seemungal TA, Bhowmik A, et al. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002; 57: 847-52
28. Fagon JY, Chastre J, Trouillet JL, et al. Characterization of distal bronchial microflora during acute exacerbation of chronic bronchitis. Am Rev Respir Dis 1990; 142: 1004-8
29. Soler N, Torres A, Ewig S, et al. Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. Am J Respir Crit Care Med 1998; 157: 1498-505
30. Pela R, Marchesani FF, Agostinelli C, et al. Airways microbial flora in COPD patients in stable clinical conditions and during exacerbations: a bronchoscopic investigation. Monaldi Arch Chest Dis 1998; 53: 262-7
31. Monso E, Ruiz J, Rosell A, et al. Bacterial infection in chronic obstructive pulmonary disease: a study of stable and exacerbated outpatients using the protected specimen brush. Am J Respir Crit Care Med 1995; 152: 1316-20
32. Sethi S, Evans N, Grant BJB, et al. New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. N Engl J Med 2002; 347: 465-71
33. Sethi S, Wrona C, Grant BJB, et al. Strain-specific immune responses to Haemophilus influenzae in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004; 169: 448-53
34. Beckham JB, Cadena A, Lin J, et al. Respiratory viral infections in patients with chronic obstructive pulmonary disease. J Infect 2005; 50: 322-30
35. Rohde G, Wiethege A, Borg I, et al. Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: a case-control study. Thorax 2003; 58: 37-42
36. Blasi F, Legnani D, Lombardo VM, et al. Chlamydia pneumoniae infection in acute exacerbations of COPD. Eur Respir J 1993; 6: 19-22
37. Beaty CD, Grayston JT, Wang SP, et al. Chlamydia pneumoniae, strain TWAR, infection in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1991; 144: 1408-10
38. Lieberman D, Lieberman D, Ben-Yaakov M, et al. Serological evidence of Mycoplasma pneumoniae infection in acute exacerbation of COPD. Diagn Microbiol Infect Dis 2002; 44: 1-6
39. MacNee W, Donaldson K. Exacerbations of COPD: environmental mechanisms. Chest 2000; 117 (5 Suppl. 2): 390S-7S
40. Sunyer J, Saez M, Murillo C, et al. Air pollution and emergency room admissions for chronic obstructive pulmonary disease: a 5-year study. Am J Epidemiol 1993; 137: 701-5
41. Mannino DM, Homa DM, Akinbami LJ, et al. Chronic obstructive pulmonary disease surveillance – United States, 1971–2000. MMWR Surveill Summ 2002; 51 (SS6): 1-16
42. National Center for Health Statistics. The National Health Interview Survey (NHIS), 1988–1994. Hyattsville (MD): Division of Health Interview Statistics, National Center for Health Statistics, Centers for Disease Control and Prevention [online]. Available from URL: http://www.cdc.gov/nchs/nhis.htm [Accessed 2006 Feb 27]
43. National Center for Health Statistics. The Third National Health and Nutrition Examination Survey (NHANES III), 1988–94. Hyattsville (MD): National Center for Health Statistics, Centers for Disease Control and Prevention [online]. Available from URL: http://www.cdc.gov/nchs/about/major/nhanes/nh3data.htm [Accessed 2006 Feb 27]
44. Anthonisen NR. Prognosis in chronic obstructive pulmonary disease: results from multicenter clinical trials. Am Rev Respir Dis 1989; 140: S95-9
45. Miravitlles M, Guerrero T, Mayordomo C, et al. Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients: a multiple logistic regression analysis. Respiration 2000; 67: 495-501
46. Roberts CM, Lowe D, Bucknall CE, et al. Clinical audit indicators of outcome following admission to hospital with acute

© 2007 Adis Data Information BV. All rights reserved.

exacerbation of chronic obstructive pulmonary disease. Thorax 2002; 57: 137-41

47. Kessler R, Faller M, Fourgaut G, et al. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999; 159: 158-64
48. Seemungal TAR, Donaldson GC, Paul EA, et al. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998; 157: 1418-22
49. Osman LM, Godden DJ, Friend JAR, et al. Quality of life and hospital re-admission in patients with chronic obstructive pulmonary disease. Thorax 1997; 52: 67-71
50. Niewoehner DE, Lokhnygina Y, Rice K, et al. Risk indices for exacerbations and hospitalizations due to COPD. Chest 2007; 131: 20-28
51. Warren PM, Flenley DC, Millar JS, et al. Respiratory failure revisited: acute exacerbations of chronic bronchitis between 1961–68 and 1970–76. Lancet 1980; 1 (8166): 467-70
52. Heuser MD, Case LD, Ettinger WH. Mortality in intensive care patients with respiratory disease: is age important? Arch Intern Med 1992; 152: 1683-8
53. Fuso L, Incalzi RA, Pistelli R, et al. Predicting mortality of patients hospitalized for acutely exacerbated chronic obstructive pulmonary disease. Am J Med 1995; 98: 272-7
54. Svartengren M, Falk R, Philipson K. Long-term clearance from small airways decreases with age. Eur Respir J 2005; 26: 609-15
55. Kikawada M, Iwamoto T, Takasaki M. Aspiration and infection in the elderly: epidemiology, diagnosis, and management. Drugs Aging 2005; 22: 115-30
56. Meyer KC. Aging. Proc Am Thorac Soc 2005; 2: 433-9
57. American Thoracic Society and European Respiratory Society standards for the diagnosis and management of patients with COPD. American Thoracic Society [online]. Available from URL: http://www.thoracic.org/sections/copd/index.html [Accessed 2007 Mar 12]
58. Proskocil BJ, Fryer AD. Beta2-agonist and anticholinergic drugs in the treatment of lung disease. Proc Am Thorac Soc 2005; 2: 305-10
59. Belmonte KE. Cholinergic pathways in the lungs and anticholinergic therapy for chronic obstructive pulmonary disease. Proc Am Thorac Soc 2005; 2: 297-304
60. Backman R, Hellstrom P. Fenoterol and ipratropium bromide for treatment of patients with chronic bronchitis. Curr Ther Res 1985; 38: 135-40
61. Rebuck AS, Chapman KR, Abboud R, et al. Nebulized anticholinergic and sympathomimetic treatment of asthma and chronic obstructive pulmonary disease in the emergency room. Am J Med 1987; 82: 59-64
62. Karpel JP, Pesin J, Greenberg D, et al. A comparison of the effects of ipratropium bromide and metaproterenol sulfate in acute exacerbations of COPD. Chest 1990; 98: 835-9
63. COMBIVENT Inhalation Solution Study Group. Routine nebulized ipratropium and albuterol together are better then either alone in COPD. Chest 1997; 112: 1514-21
64. Gross N, Tashkin D, Miller R, et al. Inhalation by nebulization of albuterol-ipratropium combination (Dey combination) is superior to either agent alone in the treatment of chronic obstructive pulmonary disease. Dey Combination Solution Study Group. Respiration 1998; 65: 354-62
65. O'Driscoll BR, Taylor RJ, Horsley MG, et al. Nebulized salbutamol with and without ipratropium bromide in acute airflow obstruction. Lancet 1989; 1: 1418-20
66. Moayyedi P, Congleton J, Page RL, et al. Comparison of nebulized salbutamol and ipratropium bromide with salbutamol alone in the treatment of chronic obstructive pulmonary disease. Thorax 1995; 50: 834-7
67. Patrick DM, Dales RE, Stark RM, et al. Severe exacerbations of COPD and asthma: incremental benefit of adding ipratropium to usual therapy. Chest 1990; 98: 295-7
68. Shrestha M, O'Brien T, Haddox R, et al. Decreased duration of emergency department treatment of chronic obstructive pulmonary disease exacerbations with the addition of ipratropium bromide to beta-agonist therapy. Ann Emerg Med 1991; 20: 1206-9
69. Berry RB, Shinto RA, Wong FH, et al. Nebulizer vs. spacer for bronchodilator therapy in patients hospitalized for acute exacerbations of COPD. Chest 1989; 96: 1241-6
70. Greene AB Jr, Jackson CL. Terbutaline metered-dose inhalation vs. metaproterenol by hand-held nebulization: a comparison in black inner-city COPD patients. J Natl Med Assoc 1988; 80: 393-6
71. Higgins RM, Cookson WO, Chadwick GA. Changes in blood gas levels after nebuhaler and nebulizer administration of terbutaline in severe chronic airway obstruction. Bull Eur Physiopathol Respir 1987; 23: 261-4
72. Jasper AC, Mohsenifar Z, Kahan S, et al. Cost-benefit comparison of aerosol bronchodilator delivery methods in hospitalized patients. Chest 1987; 91: 614-8
73. Maguire GP, Newman T, DeLorenzo LJ, et al. Comparison of a hand-held nebulizer with a metered-dose inhaler-spacer combination in acute obstructive pulmonary disease. Chest 1991; 100: 1300-5
74. Summer W, Elston R, Tharpe L, et al. Aerosol bronchodilator delivery methods: relative impact on pulmonary function and cost of respiratory care. Arch Intern Med 1989; 149: 618-23
75. Turner JR, Corkery KJ, Eckman D, et al. Equivalence of continuous flow nebulizer and metered-dose inhaler with reservoir bag for treatment of acute airflow obstruction. Chest 1988; 93: 476-81
76. Armitage JM, Williams SJ. Inhaler technique in the elderly. Age Ageing 1988; 17: 275-8
77. Connolly MJ. Inhaler technique of elderly patients: comparison of metered-dose inhalers and large volume spacer devices. Age Ageing 1995; 24: 190-2
78. Connolly MJ, Crowley JJ, Charan NB, et al. Impaired bronchodilator response to albuterol in healthy elderly men and women. Chest 1995; 108: 401-6
79. Barros MJ, Rees PJ. Bronchodilator responses to salbutamol followed by ipratropium bromide in partially reversible airflow obstruction. Respir Med 1990; 84: 371-5
80. Lipworth BJ, Tregaskis BF, McDevitt DG. Comparison of hypokalemic, electrocardiographic and hemodynamic responses to inhaled isoprenaline and salbutamol in young and elderly subjects. Eur J Clin Pharmacol 1991; 40: 255-60
81. Mandelberg A, Krupnik Z, Houri S, et al. Salbutamol metered-dose inhaler with spacer for hyperkalemia: how fast? How safe? Chest 1999; 115: 617-22
82. Breeden CC, Safirstein BH. Albuterol and spacer-induced atrial fibrillation. Chest 1990; 98: 762-3
83. Bouvy ML, Heerdink ER, DeBruin ML, et al. Use of sympathomimetic drugs leads to increased risk of hospitalization for

© 2007 Adis Data Information BV. All rights reserved.

arrhythmias in patients with congestive heart failure. Arch Intern Med 2000; 160: 2477-80
84. Anthonisen NR, Connett JE, Enright PL, et al. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med 2002; 166: 333-9
85. Pakes GE, Brogden RN, Heel RC, et al. Ipratropium bromide: a review of its pharmacological properties and therapeutic efficacy in asthma and chronic bronchitis. Drugs 1980; 20: 237-66
86. Chapman KR, Smith DL, Rebuck AS, et al. Hemodynamic effects of inhaled ipratropium bromide alone and combined with an inhaled beta2-agonist. Am Rev Respir Dis 1985; 132: 845-7
87. Pras E, Stienlauf S, Pinkhas J, et al. Urinary retention associated with ipratropium bromide. DICP 1991; 25: 939-40
88. Hall SK. Acute angle-closure glaucoma as a complication of combined beta-agonist and ipratropium bromide therapy in the emergency department. Ann Emerg Med 1994; 23: 884-7
89. Handley D. The asthma-like pharmacology and toxicology of (S)-isomers of beta agonists. J Allergy Clin Immunol 1999; 104: S69-76
90. Datta D, Vitale A, Lahiri B, et al. An evaluation of nebulized levalbuterol in stable COPD. Chest 2003; 124: 844-9
91. Nowak R, Emerman C, Hanrahan JP, et al. A comparison of levalbuterol with racemic albuterol in the treatment of acute severe asthma exacerbations in adults. Am J Emerg Med 2006; 24: 259-67
92. Scott VL, Frazee LA. Retrospective comparison of nebulized levalbuterol and albuterol for adverse events in patients with acute airflow obstruction. Am J Ther 2003; 10: 341-7
93. Lam S, Chen J. Changes in heart rate associated with nebulized racemic albuterol and levalbuterol in intensive care patients. Am J Health Syst Pharm 2003; 19: 1971-5
94. Truitt T, Witko J, Halpern M. Levalbuterol compared to racemic albuterol: efficacy and outcomes in patients hospitalized with COPD or asthma. Chest 2003; 123: 128-35
95. Cosio BG, Tsaprouni L, Ito K, et al. Theophylline restores histone deacetylase activity and steroid responsiveness in COPD macrophages. J Exp Med 2004; 200: 689-95
96. Kongragunta VR, Druz WS, Sharp JT. Dyspnea and diaphragmatic fatigue in patients with chronic obstructive pulmonary disease: responses to theophylline. Am Rev Respir Dis 1988; 137: 662-7
97. Umut S, Gemicioglu B, Yildirim N, et al. Effect of theophylline in chronic obstructive lung disease. Int J Clin Pharmacol Ther Toxicol 1992; 30: 149-52
98. Wrenn K, Slovis CM, Murphy F, et al. Aminophylline therapy for acute bronchospastic disease in the emergency room. Ann Intern Med 1991; 115: 241-7
99. Rice KL, Leatherman JW, Duane PG, et al. Aminophylline for acute exacerbation of chronic obstructive pulmonary disease: a controlled trial. Ann Intern Med 1987; 107: 305-9
100. Seidenfeld JJ, Jones WN, Moss RE, et al. Intravenous aminophylline in the treatment of acute bronchospastic exacerbations of chronic obstructive pulmonary disease. Ann Emerg Med 1984; 13: 248-52
101. Duffy N, Walker P, Diamantea F, et al. Intravenous aminophylline in patients admitted to hospital with non-acidotic exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Thorax 2005; 60: 713-7
102. Emerman CL, Devlin C, Connors AF. Risk of toxicity in patients with elevated theophylline levels. Ann Emerg Med 1990; 19: 643-8
103. Armijo JA, Sanchez BM, Peralta FG, et al. Pharmacokinetics of an ultralong sustained-release theophylline formulation when given twice daily in elderly patients with chronic obstructive pulmonary disease: monitoring implications. Biopharm Drug Dispos 2003; 24: 165-71
104. Ohnishi A, Kato M, Kojima J, et al. Differential pharmacokinetics of theophylline in elderly patients. Drugs Aging 2003; 20: 71-84
105. Barr RG, Rowe BH, Camargo CA. Methylxanthines for exacerbations of chronic obstructive pulmonary disease: a meta-analysis of randomised trials. BMJ 2003; 327: 643-8
106. Albert RK, Martin TR, Lewis SW. Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. Ann Intern Med 1980; 92: 753-8
107. Maltais F, Ostinelli J, Bourbeau J, et al. Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Am J Respir Crit Care Med 2002; 165: 698-703
108. Thompson WH, Nielson CP, Carvalho P, et al. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. Am J Respir Crit Care Med 1996; 154: 407-12
109. Aaron SD, Vandemheen KL, Hebert P, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. N Engl J Med 2003; 348: 2618-25
110. Sayiner A, Aytemur ZA, Cirit M, et al. Systemic corticosteroids in severe exacerbations of COPD. Chest 2001; 119: 726-30
111. Boston Collaborative Drug Surveillance Program. Acute adverse reactions to prednisone in relation to dosage. Clin Pharmacol Ther 1972; 13: 694-8
112. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticoids. Rev Infect Dis 1989; 11: 954-63
113. Conn HO, Poynard T. Corticosteroids and peptic ulcer: meta-analysis of adverse events during steroid therapy. J Intern Med 1994; 236: 619-32
114. Amaya-Villar R, Garnacho-Montero J, Garcia-Garmendia JL, et al. Steroid-induced myopathy in patients intubated due to exacerbation of chronic obstructive pulmonary disease. Intensive Care Med 2005; 31: 157-61
115. De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA 2002; 288: 2859-67
116. Kumar S. Steroid-induced myopathy following a single oral dose of prednisolone. Neurol India 2003; 51: 554-6
117. Dekhuijzen PN, Decramer M. Steroid-induced myopathy and its significance to respiratory disease: a known disease rediscovered. Eur Respir J 1992; 5: 997-1003
118. Alonso Martinez JL, Rubio Obanos MT, Samperiz Legarre AL, et al. Antibiotic treatment for acute episodes of chronic obstructive pulmonary disease [in Spanish]. An Med Interna 1992; 9: 377-80
119. Elmes PC, King TK, Langlands JH, et al. Value of ampicillin in the hospital treatment of exacerbations of chronic bronchitis. BMJ 1965; 5467: 904-8
120. Hansen M, Evald T, Balslov S, et al. A randomized double-blind trial between amoxycillin and placebo in the treatment of acute exacerbations of chronic bronchitis [abstract]. Eur Resp J 1990; 3 Suppl. 10: 89
121. Jørgensen AF, Coolidge J, Pedersen PA, et al. Amoxicillin in treatment of acute uncomplicated exacerbations of chronic bronchitis: a double-blind, placebo-controlled multicentre

© 2007 Adis Data Information BV. All rights reserved.

study in general practice. Scand J Prim Health Care 1992; 10: 7-11
122. Manresa F, Blavia R, Martin R, et al. Antibiotics for exacerbations of chronic bronchitis. Lancet 1987; 2: 394-5
123. Nicotra MB, Rivera M, Awe RJ. Antibiotic therapy of acute exacerbations of chronic bronchitis: a controlled study using tetracycline. Ann Intern Med 1982; 97: 18-21
124. Nouira S, Marghli S, Belghith M, et al. Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomised placebo-controlled trial. Lancet 2001; 358: 2020-5
125. Petersen ES, Esmann V, Honcke P, et al. A controlled study of the effect of treatment on chronic bronchitis: an evaluation using pulmonary function tests. Acta Med Scand 1967; 182: 293-305
126. Pines A, Raafat H, Plucinski K, et al. Antibiotic regimens in severe and acute purulent exacerbations of chronic bronchitis. BMJ 1968; 2: 735-8
127. Pines A, Raafat H, Greenfield JS, et al. Antibiotic regimens in moderately ill patients with purulent exacerbations of chronic bronchitis. Brit J Dis Chest 1972; 66: 107-15
128. Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, et al. Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2006; 2: CD004403
129. Stockley RA, O'Brien C, Pye A, et al. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. Chest 2000; 117: 1638-45
130. Barbera JA, Roca J, Ferrer A, et al. Mechanisms of worsening gas exchange during acute exacerbations of chronic obstructive pulmonary disease. Eur Respir J 1997; 10: 1285-91
131. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Ann Intern Med 1980; 93: 391-8
132. Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Lancet 1981; 1: 681-6
133. Aubier M, Murciano D, Milic-Emili J, et al. Effects of the administration of O_2 on ventilation and blood gasses in patients with chronic obstructive pulmonary disease during acute respiratory failure. Am Rev Respir Dis 1980; 122: 747-54
134. Dunn WF, Nelson SB, Hubmayr RD. Oxygen-induced hypercarbia in obstructive pulmonary disease. Am Rev Respir Dis 1991; 144: 526-30
135. Sassoon CS, Hassell KT, Mahutte CK. Hyperoxic-induced hypercapnia in stable chronic obstructive pulmonary disease. Am Rev Respir Dis 1987; 135: 907-11
136. Robinson TD, Frieberg DB, Regnis JA, et al. The role of hypoventilation and ventilation-perfusion redistribution in oxygen-induced hypercapnia during acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000; 161: 1524-9
137. Moloney ED, Kiely JL, McNicholas WT. Controlled oxygen therapy and carbon dioxide retention during exacerbations of chronic obstructive pulmonary disease. Lancet 2001; 357: 526-8
138. Agusti AG, Carrera M, Barbe F, et al. Oxygen therapy during exacerbations of chronic obstructive pulmonary disease. Eur Respir J 1999; 14: 934-9
139. Plant PK, Owen JL, Elliott MW. One year period prevalence study of respiratory acidosis in acute exacerbations of COPD: implications for the provision of non-invasive ventilation and oxygen administration. Thorax 2000; 55: 550-4
140. Gomersall CD, Joynt GM, Freebairn RC, et al. Oxygen therapy for hypercapnic patients with chronic obstructive pulmonary disease and acute respiratory failure: a randomized, controlled pilot study. Crit Care Med 2002; 30: 113-6
141. Takeuchi T, Matsushima E, Moriya H, et al. Delirium in inpatients with respiratory diseases. Psychiatry Clin Neurosci 2005; 59: 253-8
142. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. JAMA 1990; 263: 1097-101
143. Ram FSF, Picot J, Lighttowler J, et al. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2004; 3: CD004104
144. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med 1995; 333: 817-22
145. Celikel T, Sungur M, Ceyhan B, et al. Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic acute respiratory failure. Chest 1998; 114: 1636-42
146. Conti G, Antonelli M, Navalesi P, et al. Noninvasive vs. conventional mechanical ventilation in patients with chronic obstructive pulmonary disease after failure of medical treatment in the ward: a randomized trial. Intensive Care Med 2002; 28: 1701-7
147. Kramer N, Meyer TJ, Meharg J, et al. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. Am J Resp Crit Care Med 1995; 151: 1799-806
148. Servillo G, Ughi L, Rossano F, et al. Non invasive mask pressure support ventilation in COPD patients [abstract]. Intensive Care Med 1994; 20 Suppl. 2: S54
149. Thys F, Roeseler J, Reynaert M, et al. Noninvasive ventilation for acute respiratory failure: a prospective randomised placebo-controlled trial. Eur Respir J 2002; 20: 545-55
150. Avdeev SN, Tretyakov AV, Grigoryants RA, et al. Noninvasive positive airway pressure ventilation: role in treating acute respiratory failure caused by chronic obstructive pulmonary disease [in Russian]. Anesteziol Reanimatol 1998; 3: 45-51
151. Barbe R, Togores B, Rubi M, et al. Noninvasive ventilatory support does not facilitate recovery from acute respiratory failure in chronic obstructive pulmonary disease. Eur Respir J 1996; 9: 1240-5
152. Bott J, Keilty SEJ, Elliott MW, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive pulmonary disease. Lancet 1993; 341: 1555-7
153. del Castillo D, Barrot E, Laserna E, et al. Noninvasive positive pressure ventilation for acute respiratory failure in chronic obstructive pulmonary disease in a general respiratory ward [in Spanish]. Medicina Clin (Barc) 2003; 120: 647-51
154. Dikensoy O, Ikidag B, Filiiz A, et al. Comparison of noninvasive ventilation and standard medical therapy in acute hypercapnic respiratory failure: a randomised controlled trial at a tertiary health centre in SE Turkey. Int J Clin Pract 2002; 56: 85-8
155. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. Lancet 2000; 355: 1931-5
156. Zhou R, Chen P, Luo H, et al. Effects of noninvasive positive pressure ventilation on gas exchange and patients' transformation in chronic obstructive pulmonary disease and respiratory failure [in Chinese]. Bull Hunan Med Univ 2001; 26: 261-2

© 2007 Adis Data Information BV. All rights reserved.

157. Khilnanai GC, Saikia N, Sharma SK, et al. Efficacy of non-invasive positive pressure ventilation (NPPV) for management of COPD with acute or acute on chronic respiratory failure: a randomized controlled trial [abstract]. Am J Respir Crit Care Med 2002; 165 Suppl.: A387
158. Putinati S, Ballerin L, Piatella M, et al. Is it possible to predict the success of non-invasive ventilation in acute respiratory failure due to COPD? Resp Med 2000; 94: 991-1001
159. Soo Hoo GW, Santiago S, Williams AJ. Nasal mechanical ventilation for hypercapnic respiratory failure in chronic obstructive pulmonary disease: determinants of success and failure. Crit Care Med 1994; 22: 1253-61
160. Ambrosino N, Foglio K, Rubini F, et al. Non-invasive mechanical ventilation in acute respiratory failure due to chronic obstructive pulmonary disease: correlates for success. Thorax 1995; 50: 755-7
161. Mehta S, Hill NS. Noninvasive ventilation. Am J Respir Crit Care Med 2001; 163: 540-77
162. Behrendt CE. Acute respiratory failure in the United States: incidence and 31-day survival. Chest 2000; 118: 1100-5
163. Esteban A, Anzueto A, Frutos F, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 2002; 287: 345-55
164. Suissa S. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006; 173: 842-6
165. Scott S, Walker P, Calverley PMA. COPD exacerbations – 4: prevention. Thorax 2006; 61: 440-7
166. Sin DD, McAlister FA, Man SFP, et al. Contemporary management of chronic obstructive pulmonary disease: scientific review. JAMA 2003; 290: 2301-12
167. Wilt TJ, Niewoehner D, Kim C, et al. Use of spirometry for case finding, diagnosis, and management of chronic obstructive pulmonary disease (COPD). Evidence report/technology assessment No. 121. Prepared by the Minnesota Evidence-based Practice Center under contract No. 290-02-0009. AHRQ Publication No. 05-E017-2. Rockville (MD). Agency for Healthcare Research and Quality, 2005 Sep [online]. Available from URL: http://www.ahrq.gov/downloads/pub/evidence/pdf/spirocopd/spiro.pdf [Accessed 2007 Feb 28]
168. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1: the Lung Health Study. JAMA 1994; 272: 1497-505
169. Burchfiel CM, Marcus EB, Curb JD, et al. Effects of smoking and smoking cessation on longitudinal decline in pulmonary function. Am J Respir Crit Care Med 1995; 151: 1778-85
170. Pelkonen M, Notkola IL, Tukiainen H, et al. Smoking cessation, decline in pulmonary function and total mortality: a 30 year follow up study among the Finnish cohorts of the Seven Countries Study. Thorax 2001; 56: 703-7
171. Godtfredsen NS, Vestbo J, Osler M, et al. Risk of hospital admission for COPD following smoking cessation and reduction: a Danish population study. Thorax 2002; 57: 967-72
172. Anthonisen NR, Skeans MA, Wise RA, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med 2005; 142: 233-9
173. Buckland A, Connolly MJ. Age-related differences in smoking cessation advice and support given to patients hospitalised with smoking-related illness. Age Ageing 2005; 34: 639-42
174. Fiore MC, Bailey WC, Cohen SJ, et al. Treating tobacco use and dependence: clinical practice guideline. Rockville (MD): US Department of Health and Human Services. Public Health Service, 2000 Jun
175. West R, McNeill A, Raw M. Smoking cessation guidelines for health professionals: an update: Health Education Authority. Thorax 2000; 55: 987-99
176. Anderson JE, Jorenby DE, Scott WJ, et al. Treating tobacco use and dependence: an evidence-based clinical practice guideline for tobacco cessation. Chest 2002; 121: 932-41
177. Appleton S, Poole P, Smith B, et al. Long-acting beta2-agonists for poorly reversible chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2006; 3: CD001104
178. Boyd G, Morice AH, Pounsford JC, et al. An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). Eur Respir J 1997; 10: 815-21
179. Celli B, Halpin D, Hepburn R, et al. Symptoms are an important outcome in chronic obstructive pulmonary disease clinical trials: results of a 3-month comparative study using the Breathlessness, Cough and Sputum Scale (BCSS). Respir Med 2003; 97 Suppl. 1: S35-43
180. Chapman KR, Arvidsson P, Chuchalin AG, et al. The addition of salmeterol 50μg bid to anticholinergic treatment in patients with COPD: a randomized, placebo controlled trial. Can Respir J 2002; 9: 178-85
181. van Noord JA, de Munck DR, Bantje TA, et al. Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium. Eur Respir J 2000; 15: 878-85
182. Barr RG, Bourbeau J, Camargo CA, et al. Tiotropium for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005; 2: CD002876
183. Beeh KM, Beier J, Stark-Lorenzen P, et al. Efficacy of tiotropium (Spiriva) in COPD of different severities [abstract] (in German). Pneumologie 2004; 58: S43
184. Brusasco V, Hodder R, Miravitlles M, et al. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax 2003; 58: 399-404
185. Calverley PMA, Lee A, van Noord J, et al. Effect of tiotropium bromide on circadian variation in airflow limitation in chronic obstructive pulmonary disease. Thorax 2003; 58: 855-60
186. Casaburi R, Malher DA, Jones PW, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J 2002; 19: 217-24
187. Celli B, Wallack RZ, Wang S, et al. Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. Chest 2003; 124: 1743-8
188. Littner MR, Ilowite JS, Tashkin DP, et al. Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva) in stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000; 161: 1136-42
189. Niewoehner DE, Rice K, Cote C, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. Ann Intern Med 2005; 143: 317-26
190. O'Donnell DE, Fluge T, Gerken F, et al. Effects of tiotropium on lung hyperinflation, dyspnoea, and exercise tolerance in COPD. Eur Respir J 2004; 23: 832-40
191. Calverley PM. Inhaled corticosteroids are beneficial in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000; 161: 341-2

© 2007 Adis Data Information BV. All rights reserved.

192. Barnes PJ. Inhaled corticosteroids are not beneficial in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000; 161: 342-4

193. Alsaeedi A, Sin DD, McAlister FA. The effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a systematic review of randomized placebo-controlled trials. Am J Med 2002; 113: 59-65

194. Gartlehner G, Hansen RA, Carson SS, et al. Efficacy and safety of inhaled corticosteroids in patients with COPD: a systematic review and meta-analysis of health outcomes. Ann Fam Med 2006; 4: 253-62

195. Bourbeau J, Rouleau MY, Boucher S. Randomised controlled trial of inhaled corticosteroids in patients with chronic obstructive pulmonary disease. Thorax 1998; 53: 477-82

196. Burge PS, Calverley PM, Jones PW, et al. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000; 320: 1297-303

197. Paggiaro PL, Dahle R, Bakran I, et al. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease: International COPD Study Group. Lancet 1998; 351: 773-80

198. Vestbo J, Sorensen T, Lange P, et al. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 1999; 353: 1819-23

199. Leech JA, Gervais A, Ruben FL. Efficacy of pneumococcal vaccine in severe chronic obstructive pulmonary disease. CMAJ 1987; 136: 361-5

200. Franzen D. Clinical efficacy of pneumococcal vaccination: a prospective study in patients with longstanding emphysema and/or bronchitis. Eur J Med Res 2000; 5: 537-40

201. Nichol KL, Baken L, Wuorenma J, et al. The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease. Arch Intern Med 1999; 159: 2437-342

202. Alfageme I, Vazquez R, Reyes N, et al. Clinical efficacy of antipneumococcal vaccination in patients with COPD. Thorax 2006; 61: 189-95

203. Centers for Disease Control and Prevention. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 1997; 46 (RR-8): 1-24

204. Howells CHL, Tyler LE. Prophylactic use of influenza vaccine in patients with chronic bronchitis: a pilot trial. Lancet 1961; 2: 1428-32

205. Wongsurakiat P, Maranetra KN, Wasi C, et al. Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: a randomized controlled study. Chest 2004; 125: 2011-20

206. Nichol KL, Baken L, Nelson A. Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease. Ann Intern Med 1999; 130: 397-403

207. Poole PJ, Chacko E, Wood-Baker RW, et al. Influenza vaccine for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2006; 1: CD002733

208. Wongsurakiat P, Maranetra KN, Gulprasutdilog P, et al. Adverse effects associated with influenza vaccination in patients with COPD: a randomized controlled study. Respirology 2004; 9: 550-6

209. Tata LJ, West J, Harrison T, et al. Does influenza vaccination increase consultations, corticosteroid prescriptions, or exacerbations in subjects with asthma or chronic obstructive pulmonary disease? Thorax 2003; 58: 835-9

210. Poole PJ, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2006; 3: CD001287

211. Decramer M, Rutten-van Molken M, Dekhuijzen PN, et al. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. Lancet 2005; 365: 1552-60

212. Foglio K, Bianchi L, Bruletti G, et al. Long-term effectiveness of pulmonary rehabilitation in patients with chronic airway obstruction. Eur Respir J 1999; 13: 125-32

213. Griffiths TL, Burr ML, Campbell IA, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet 2000; 355: 362-8

214. Guell R, Casan P, Belda J, et al. Long-term effects of outpatient rehabilitation of COPD: a randomized trial. Chest 2000; 117: 976-83

215. Foglio K, Bianchi L, Ambrosino N. Is it really useful to repeat outpatient pulmonary rehabilitation programs in patients with chronic airway obstruction? A 2-year controlled study. Chest 2001; 119: 1696-704

216. Taylor SJ, Candy B, Bryar RM, et al. Effectiveness of innovations in nurse led chronic disease management for patients with chronic obstructive pulmonary disease: systematic review of evidence. BMJ 2005; 331: 485-91

217. Bourbeau J, Julien M, Maltais F, et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. Arch Intern Med 2003; 163: 585-91

218. Casas A, Troosters T, Garcia-Aymerich J, et al. Integrated care prevents hospitalizations for exacerbations in COPD patients. Eur Respir J 2006; 28: 123-30

Correspondence: Dr *Dennis E. Niewoehner*, Pulmonary Section (111N), Veterans Affairs Medical Center, 1 Veterans Drive, Minneapolis, MN 55417, USA.
E-mail: niewo001@umn.edu

© 2007 Adis Data Information BV. All rights reserved.