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Acute Exacerbations in Chronic Obstructive Pulmonary Disease

Current Strategies with Pharmacological Therapy

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Abstract

In acute exacerbation of chronic obstructive pulmonary disease (AECOPD), short-acting inhaled bronchodilators, such as salbutamol (albuterol) and ipratropium bromide, have proven useful. In patients who are refractory to these agents, intravenous aminophylline should be considered. Corticosteroids should also be used, either in the outpatient or inpatient setting. The duration of corticosteroids should probably not exceed 2 weeks and the optimum dosage is yet to be determined. Antibacterials, especially in patients with purulent or increased sputum, should be used, guided by the local antibiogram of the key microbes. Controlled oxygen therapy improves outcome in hypoxaemic patients and arterial blood gases should be performed to ensure hypercarbia is not becoming excessive. Should patients be in distress despite the above measures or if there is acidaemia or hypercarbia, noninvasive positive pressure ventilation could be used to improve outcomes without resorting to invasive mechanical ventilation. Mucous-clearing drugs and chest physiotherapy have no proven beneficial role in AECOPD.

Chronic obstructive pulmonary disease (COPD) is a significant health problem affecting at least 52 million people worldwide. It is currently the fourth leading cause of death and the 12th leading cause of

morbidity in the world.[1,2] It represents a significant economic burden to countries throughout the world, costing the UK $US4 billion in 1996 and the US $US23 billion in 1993.

COPD is defined as a disease characterised by chronic airflow limitation that is not fully reversible.[2] The obstruction is usually progressive and is associated with an abnormal inflammatory response to noxious stimuli. Acute exacerbations of COPD (AECOPD) are generally defined as symptoms of increased breathlessness with increased volume or purulence of sputum.[3] Patients may or may not have hypoxaemia and hypercarbia. People with COPD have, on average, 2–4 exacerbations per year.[4] Active smokers tend to have more exacerbations per year than non-smokers; data has shown that smoking cessation can decrease the frequency of exacerbations by about one-third.[5] A commonly used grading system for the severity of AECOPD was developed by Anthonisen et al.[6] (table I). Criteria for hospitalisation as recommended in the Global initiative for chronic Obstructive Lung Disease (GOLD) report[2] include increased symptoms, severe disease, new physical mean signs, older age, insufficient home support and other co-morbidities. These are guidelines recommended by an expert panel and up to the discretion of the individual physician.

AECOPD can be triggered by a number of different stimuli. Tracheobronchial infections are often associated with exacerbations. Sputum from patients with COPD often grow *Haemophilus influenzae*, *Pseudomona aeruginosa*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*.[7] In addition, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and viruses have been implicated. The exact role of these microbes in the pathogenesis of AECOPD is still unclear. Non-infectious environmental exposures (e.g. dust, gases and pollution) and ozone have also been implicated. Finally, other medical conditions such as heart failure, pulmonary embolism, pneumothorax and non-pulmonary infections can play a role.[8]

Table I. Grading the severity of acute exacerbation of chronic obstructive pulmonary disease[6]

Grade of severity (type)	Symptoms of exacerbation
Severe (type 1)	All three symptoms[a]
Moderate (type 2)	Two out of three symptoms[a]
Mild (type 3)	One out of three symptoms,[a] plus one of the following: fever with no other cause, increase in wheeze, increase in cough, increase in respiration or heart rate by 20%

a Symptoms include: (i) increased dyspnea; (ii) increased volume of sputum; and (iii) purulence of sputum.

Defining optimal treatment strategies for AECOPD has been difficult because of different definitions of what constitutes AECOPD and different outcomes used to define success. This article provides a summary of the current data relating to the treatment of AECOPD, with a special emphasis on the role of bronchodilator therapy. The treatment regimens for stable COPD are beyond the scope of this article. However, the agents that are chosen to treat an exacerbation may vary depending upon the patient's maintenance therapy at the time of exacerbation.

1. Bronchodilator Therapy

Bronchodilator therapy refers to the use of β_2-adrenoceptor agonists, anticholinergic agents and methylxanthines (theophylline, aminophylline).

1.1 β_2-Adrenoceptor Agonists and Anticholinergics

β_2-adrenoceptor agonists and anticholinergics have been shown to improve airflow during AECOPD.[3] Table II provides a list of β_2-adrenoceptor agonists and anticholinergics, and their recommended doses for the treatment of AECOPD. The authors of the GOLD report recommend short-acting inhaled β_2-adrenoceptor agonists as the preferred bronchodilators for AECOPD.[2] If no response is seen, they recommend the addition of an

Table II. Commonly used β_2-adrenoceptor agonists and anticholinergic agents for the treatment of acute exacerbation of chronic pulmonary disease

Drug	Dose with hand-held nebulizer (mg)	Dose with metered dose inhaler (μg)	Dose with oral formulation (mg)	Duration of action (h)
β_2-adrenoceptor agonists				
Salbutamol (albuterol)	2.5–5.0	100–200	4	4–6[a]
Formoterol	NA	12–24	NA	>12[b]
Salmeterol	NA	50–100	NA	>12
Terbutaline	5–10	250–500	5	4–6
Fenoterol	0.5–2.0	100–200	NA	4–6
Anticholinergic agents				
Ipratropium bromide	0.25–0.5	40–80	NA	6–8
Oxitropium bromide	NA	200	NA	7–9
Tiotropium bromide[c]	NA	18	NA	>24

a Short-acting β-adrenoceptor agonist given up to 4 times daily.

b Long-acting β-adrenoceptor agonist given twice daily.

c Not available in all countries.

NA = not available in this preparation.

anticholinergic. The American College of Physicians-American Society of Internal Medicine (ACP-ASIM) in a joint position paper with the American College of Chest Physicians (ACCP) concluded that short acting β_2-adrenoceptor agonists and anticholinergic inhalers have similar effects.[9] They also believe that the use of a second agent may be beneficial if the first is not effective. A recent meta-analysis supported using an inhaled anticholinergic as first-line therapy, with the addition of a β_2-adrenoceptor agonist if needed.[10] Many investigators have looked at the benefit of one versus two bronchodilating agents in AECOPD.

The Combivent®[1] Inhalation Study Group found the combination of salbutamol (albuterol) and ipratropium bromide was more beneficial in severe COPD than either alone.[11] In these 652 patients, spirometric responses to bronchodilators and evening peak expiratory flow was significantly improved using combination therapy. There was no increase in adverse effects with either drug. Investigators in Canada found similar results comparing salbutamol alone versus combination with the anticholinergic glycopyrrolate. In this study, 57 patients attending an emergency room for AECOPD were found to have a better forced expiratory volume in 1 second (FEV_1) with combination therapy.[12] An earlier study on emergency room patients with AECOPD have also found a benefit with combination therapy.[13]

However, not all authors have found benefits with combination therapy. Moayyedi et al.[14] compared salbutamol alone and with ipratropium bromide in 70 patients with AECOPD. They found no difference between the two groups with regards to spirometry, length of stay in the hospital or symptoms of COPD. A group in Melbourne, also comparing salbutamol with and without ipratropium bromide, found similar results.[15]

Despite these conflicting results, it is common practice with AECOPD to use combination therapy of these short-acting agents, especially if there is little response to a single drug. These medications can be delivered via either hand-held nebulizers or metered dose inhalers. In a randomised trial, Maguire et al.[16] compared the efficacy of a β_2-adre-

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

noceptor agonist delivered via a hand-held nebulizer versus a metered dose inhaler with a spacer in patients with acute exacerbations of pulmonary disease. In the subgroup of patients with COPD, delivery via a hand-held nebulizer resulted in greater improvements in spirometric values. This study was small and the authors postulated that this positive result could be related to the lower dose of the β_2-adrenoceptor agonist available in the metered dose inhaler. In a meta-analysis of publications ranging from 1966–1994, Turner et al.[17] came to a different conclusion. When reviewing studies that included patients with exacerbations of asthma or COPD, they found no significant difference in efficacy between hand-held nebulizers and metered dose inhalers with a spacer. The authors concluded that the choice of delivery should be based on the availability of resources. The ACP-ASIM/ACCP position paper on AECOPD found no evidence to recommend one mode of delivery over another.[9] However, patients with AECOPD may be unable to coordinate the use of a metered dose inhaler and we will generally start therapy with hand-held nebulizers when patients first present with symptoms.

Long-acting β_2-adrenoceptor agonists (salmeterol, formoterol) have found a place in the treatment of stable COPD.[2] They are more expensive than the short-acting β_2-adrenoceptor agonist but are more convenient. D'Urzo et al.[18] found that, in patients with stable COPD, a combination of ipratropium bromide and formoterol was more efficacious than ipratropium bromide and salbutamol with regards to peak flow and symptom scores. The safety profiles of the two combination therapies were equivocal. Other authors have found improved quality of life with long-acting β_2-adrenoceptor agonists.[19] However, despite their utility in stable COPD, the use of long-acting β_2-adrenoceptor agonists in AECOPD cannot be recommended at this time.

Tiotropium bromide, a long-acting anticholinergic, has been developed for use in COPD.[20] Laboratory studies on the human lung have shown it to be 10-fold more potent than ipratropium bromide.[20] A recent randomised controlled trial found tiotropium bromide once daily to be superior to salmeterol twice daily in terms of bronchodilation, symptoms and quality of life.[21] In this study patients had stable COPD; there is currently no evidence that tiotropium bromide should be used in AECOPD.

Another category of bronchodilators is the methylxanthines. Aminophylline is available in both intravenous and oral formulations, while theophylline is available in an oral preparation only. Table III provides the recommended doses of these agents for use in AECOPD. The role of these drugs in AECOPD is unclear. The GOLD report recommends the use of aminophylline if needed in severe AECOPD after β_2-adrenoceptor agonists or anticholinergics.[2] Earlier investigations have found equivocal results with aminophylline. One study by Wrenn et al.[22] found that intravenous aminophylline in addition to β_2-adrenoceptor agonists and corticosteroids decreased hospital admissions for AECOPD and asthma. In contrast, other researchers have found that using aminophylline provided no added benefit to standard bronchodilators.[23]

Theophylline is not recommended for a patient in the midst of an exacerbation. There are multiple adverse effects of methylxanthines including vascular dilatation, increased salt and water excretion, CNS stimulation, irritability and cardiac arrhythmias.[24] These limitations often steer physicians away from prescribing these drugs. Given the questionable benefit and the adverse effect profile, aminophylline should be used as a second-line agent after inhaled bronchodilators.

Table III. Methylxanthines for the treatment of acute exacerbation of chronic pulmonary disease

Drug	Formulation	Dose
Aminophylline	Intravenous	0.9 mg/kg/h
	Oral	225–450mg
Theophylline	Oral	100–400mg

In summary, patients presenting with AECOPD should be given short-acting inhaled bronchodilators in the doses recommended in this article. There is enough evidence in the literature that combination therapy with β_2-adrenoceptor agonists and anticholinergics is effective and certainly has a good safety profile. Aminophylline should be reserved for refractory cases not responding to inhaled medications.

2. Corticosteroids

Systemic corticosteroids are increasingly used in AECOPD and are recommended in the GOLD report[2] and the ACP-ASIM/ACCP[9] guidelines. There is much evidence regarding their efficacy in AECOPD. A recent, large Veteran Affairs Cooperative Study found that corticosteroids reduced the number of treatment failures (defined as death from any cause or the need for mechanical ventilation) and length of hospitalisations.[25] A group in the UK looked at 56 hospitalised patients with AECOPD and found that oral prednisolone 30mg once daily for 2 weeks improved spirometry and reduced hospital length of stay.[26] Thompson et al.[27] found that using oral corticosteroids in the outpatient treatment of AECOPD improved gas exchange, spirometry and symptoms.

The length of treatment necessary has been debated in the literature. The Veteran Affairs Cooperative Study found that an 8-week regimen of corticosteroids was not superior to a 2-week regimen.[25] In contrast, however, a more recent study in Turkey compared a 3-day regimen of methylprednisolone with a 10-day regimen and found the longer regimen to be superior.[28] The GOLD report recommends the use of a 10-day regimen and recommends against long-term treatment with systemic corticosteroids. Long-term corticosteroids can cause steroid myopathy which contributes to muscle weakness and respiratory failure.[29] It appears that a short course of systemic corticosteroids is warranted in patients with moderate to severe AECOPD (see table IV for dosages). The optimal dosage for systemic corticosteroids in the treatment of COPD has not been clearly stablished in the literature; various randomised trials have used dosages ranging from 20 mg/day of methylprednisolone (equivalent) to 500 mg/day. Despite the evidence supporting the use of inhaled corticosteroids in stable COPD, no conclusion can be made regarding inhaled corticosteroids use in AECOPD beyond their role in reducing frequency of exacerbations.

3. Antibacterials

As mentioned in the introduction, bacterial colonisation/infection is implicated in causing AECOPD in many patients. Therefore, it seems intuitive to treat these patients with antibacterials, however, the data in the literature is controversial. A study by Adams et al.[30] found that antibacterial therapy in AECOPD decreased relapse rates. Reviewing placebo-controlled trials that were conducted between 1957–1999, Russo and D'Aprile[31] found four placebo controlled trials and a meta-analysis of AECOPD patients that demonstrated benefits with antibacterials versus placebo. However, this analysis found that six studies failed to show a difference.[31] The GOLD report recommends antibacterials for patients with AECOPD who have increased sputum or purulence in addition to dyspnea. This is the criterion Anthonisen et al.[6] used in their randomised, controlled trial of AECOPD in which they found antibacterials to be beneficial. The ACP-ASIM/ACCP position paper

Table IV. Corticosteroids used for the treatment of acute exacerbation of chronic obstructive pulmonary disease[a]

Drug	Formulation	Dose
Methylprednisolone	Intravenous	125mg every 6h
Hydrocortisone	Intravenous	100mg every 24h
Prednisone	Oral	60mg every 24h

a All for maximum 2-week course.

concluded that antibacterials are more beneficial for severe exacerbations.[9]

The choice of antibacterial agent has also been controversial. The main microbes associated with AECOPD are *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. Local resistance patterns should be known. There has been increased resistance to the traditional first-line antibacterials (such as amoxicillin, tetracycline, cotrimoxazole [trimethoprim/sulfamethoxazole]) and many recommend the use of second-line drugs such as cephalosporins, second-generation macrolides or fluoroquinolones.[32] The optimum duration of therapy has not been determined conclusively and can range from 3–14 days. Some of the antibacterials commonly used for AECOPD and their respective recommended dosages are shown in table V.

4. Oxygen Therapy/Noninvasive Positive Pressure Ventilation

Oxygen therapy has been found to be beneficial in hypoxaemic patients with AECOPD. Both the GOLD report [2] and the ACP-ASIM/ACCP guidelines[9] stress the importance of controlled oxygen therapy to keep oxygen saturation in the normal range. While hypercarbia can ensue from supplemental oxygen administration in COPD patients, studies[8] (some conducted in the 1960s) have shown that if the oxygen administration is controlled (such as with a venturi mask) the degree of hypercarbia is usually not clinically relevant. Controlled oxygen should be used in all hypoxaemic AECOPD patients.

Table V. Commonly used antibacterials for the treatment of acute exacerbation of chronic obstructive pulmonary disease

Drug	Formulation	Dose
Azithromycin	Intravenous	500mg every day
	Oral	500mg first day then 250mg every day
Amoxicillin	Oral	500mg three times daily
Ciprofloxacin	Oral	250–500mg every day
Levofloxacin	Oral	250–500mg every day
Gatifloxacin	Oral	400mg every day
Moxifloxacin	Oral	400mg every day
Tetracycline	Oral	250–500mg four times daily
Cotrimoxazole (trimethoprim/ sulfamethoxazole)	Oral	1 double-strength tablet twice daily

The benefit of noninvasive positive pressure ventilation (NPPV) in AECOPD is also well documented. Brochard et al.[33] found that NPPV given to patients with AECOPD reduced the need for endotracheal intubation, the length of hospital stay and the in-hospital mortality. More recently, the benefits of NPPV in terms of respiratory rates, pH levels, reduction in intubation, reduction in mortality and improved costs have been observed.[34-36] Patients with a decreased pH levels and hypercarbia are the best candidates for NPPV.

5. Mucous-Clearing Therapies

Pharmacological mucous-clearing agents include carbocisteine (S-carboxymethylcysteine), potassium iodide, ambroxol, bromhexine and domiodol. None of these has been shown to be of clinical benefit in randomised controlled trials.[37] Postural drainage and chest physiotherapy has also been studied in AECOPD. No trial has shown physical drainage to be of clinical benefit and one trial even showed worse FEV_1 with chest percussion therapy.[38] However, the GOLD report concludes that physical methods may be beneficial in patients producing >25 mL/day of sputum or with lobar atelectasis.[2]

6. Conclusion

In AECOPD, short-acting inhaled bronchodilators in combination have proven useful. In patients who are refractory to these agents, intravenous aminophylline should be considered. Systemic corticosteroids should also be used, either in the outpatient or inpatient setting. The duration of corticosteroid therapy should probably not exceed 2 weeks.

Antibacterials, especially in patients with purulent or increased sputum, should be used, guided by the local antibiogram of the key microbes. Controlled oxygen therapy improves outcomes in hypoxaemic patients. An arterial blood gas should be performed to ensure hypercarbia is not becoming excessive. If patients are in distress despite these measures, NPPV could be used to improve outcomes without resorting to invasive mechanical ventilation. Mucous-clearing drugs and chest physiotherapy have not proven beneficial role in AECOPD.

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References

1. Murray CJ, Lopez AD. Global morality, disability and the contribution of risk factors: global burden of disease study. Lancet 1997; 349: 1436-42
2. Pauwels RA, Buist AS, Calverley PMA, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary. Am J Resp Crit Care Med 2001; 163: 1256-76
3. Stoller JK. Acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med 2002; 346: 988-94
4. Seemungal TAR, Donaldson GC, Bhowmik A, et al. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. Am J Resp Crit Care Med 2000; 161: 1608-13
5. Kanner RE, Anthonisen NR, Connett JE. Lower respiratory illnesses promote FEV_1 decline in current smokers but not ex-smokers with mild chronic obstructive pulmonary disease: results from the Lung Health Study. Am J Resp Crit Care Med 2001; 164: 358-64
6. Anthonisen NR, Manfreda J, Warren CP, et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987; 106: 196-204
7. Miravitlles M, Espinosa C, Fernandez-Laso E, et al. Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbation of COPD. Chest 1999; 116: 40-6
8. McCrory DC, Brown C, Gelfand SE, et al. Management of acute exacerbations of COPD: a summary and appraisal of published evidence. Chest 2001; 119: 1190-209
9. Bach PB, Brown C, Gelfand SE, et al. Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. Ann Intern Med 2001; 134: 600-20
10. Snow V, Lascher S, Mottur-Pilson C. Evidence base for management of exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 2001; 134: 595-9
11. COMBIVENT Study Group Investigators. Routine nebulized ipratropium and albuterol together are better than either alone in COPD. Chest 1997; 112: 1514-21
12. Cydulka RK, Emerman CL. Effects of combined treatment with glycopyrrolaate and albuterol in acute exacerbations of chronic obstructive pulmonary disease. Ann Emerg Med 1995; 25: 470-3
13. 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 β-agonist therapy. Ann Emerg Med 1991; 20: 1206-9
14. Moayyedi P, Congleton J, Page RL, et al. Comparison of nebulised salbutamol and ipratropium bromide with salbutamol alone in the treatment of chronic obstructive pulmonary disease. Thorax 1995; 50: 834-7
15. Koutsogiannis Z, Kelly AM. Does high dose ipratropium bromide added to salbutamol improve pulmonary function for patients with chronic obstructive airways disease in the emergency department? Aust N Z J Med 2000; 30: 38-40
16. 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
17. Turner MO, Patel A, Ginsburg S, et al. Bronchodilator delivery in acute airflow obstruction: a meta-analysis. Arch Intern Med 1997; 157: 1736-44
18. D'Urzo AD, De Salvo MC, Ramirez-Rivera A, et al. In patients with COPD, treatment with a combination of formoterol and ipratropium is more effective than a combination of salbutamol and ipratropium. Chest 2001; 119: 1347-56
19. Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. Am J Resp Crit Care Med 1997; 155: 1283-9
20. Barnes PJ. The pharmacological properties of tiotropium. Chest 2000; 117 (2 Suppl.): 63S-6S
21. Donohue JF, van Noord JA, Bateman ED, et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. Chest 2002; 122: 47-55
22. Wrenn K, Slovis C, Murphy F, et al. Aminophylline therapy for acute bronchospastic disease in the emergency room. Ann Intern Med 1991; 115: 241-7
23. Rice KL, Leatherman JW, Duane PG, et al. Aminophylline for acute exacerbations of chronic obstructive pulmonary disease: a controlled trial. Ann Intern Med 1987; 107: 305-9
24. Cazzola M, Donner CF, Matera MG. Long-acting beta(2) agonists and theophylline in stable chronic obstructive pulmonary disease. Thorax 1999; 54 (8): 730-6
25. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease: Department of Veteran Affairs Cooperative Study. N Engl J Med 1999; 340 (25): 1941-7

26. Davies L, Angus RM, Calverley PMA. Oral corticosteroids in patients admitted to hospital wit exacerbations of chronic obstructive pulmonary disease: a prospective randomized controlled trial. Lancet 1999; 354: 456-60

27. Thompson WH, Nielson CP, Carvalho P, et al. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. Am J Resp Crit Care Med 1996; 154: 407-12

28. Sayner A, Aytemur ZA, Cirit M, et al. Systemic glucocorticoids in severe exacerbations of COPD. Chest 2001; 119: 726-30

29. Decramer M, Lacquet LM, Fargard R, et al. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. Am J Resp Crit Care Med 1994; 150: 11-6

30. Adams SG, Melo J, Luther M, et al. Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of COPD. Chest 2000; 117: 1345-52

31. Russo RL, D'Aprile M. Role of antimicrobial therapy in acute exacerbations of chronic obstructive pulmonary disease. Ann Pharmacother 2001; 35: 576-81

32. Grossman R, Mukherjee J, Vaughan D, et al. A 1-year community-based health economic study of ciprofloxacin vs usual antibiotic treatment in acute exacerbations of chronic bronchitis. The Canadian Ciprofloxacin Health Economic Study Group. Chest 1998; 113: 131-41

33. 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

34. Plant PK, Owen JL, Elliot MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicenter randomized controlled trial. Lancet 2000; 355: 1931-5

35. Plant PK, Owen JL, Elliot MW. Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: long term survival and predictors of in-hospital outcome. Thorax 2001; 56: 708-12

36. Keenan SP, Gregor J, Sibbald WJ, et al. Noninvasive positive pressure ventilation in the setting of severe, acute exacerbations of chronic obstructive pulmonary disease: more effective and less expensive. Crit Care Med 2000; 28: 2094-102

37. Siafakas NM, Vermeire P, Pride NB, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J 1995; 8 (8): 1398-420

38. Wollmer P, Ursing K, Midgren B, et al. Inefficiency of chest percussion in the physical therapy or chronic bronchitis. Eur J Respir Dis 1985; 66: 233-9

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