These guidelines have been replaced by NICE Guideline Chronic Obstructive Pulmonary Disease CG101

Superseded By NICE Guideline Chronic Obstructive Pulmonary Disease CG101: Chronic Obstructive Pulmonary Disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 2004 Mar; 59(Suppl 1): 1-232.

Chronic Obstructive Pulmonary Disease: Management of adults with Chronic Obstructive Pulmonary Disease in Primary and Secondary Care

Management of exacerbations of COPD
Hospital at home and assisted discharge schemes
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Hospital at home

Author	Publication Date	ID
Davies, L., Wilkinson, M., Bonner, S., Calverley, P. M., & Angus, R. M. 2000, ""Hospital at home" versus hospital care in patients with exacerbations of chronic obstructive pulmonary disease: prospective randomised controlled trial", *BMJ*, vol. 321, pp. 1265-1268.	2000	1059
Fried, T. R., Van Doorn, C., Tinetti, M. E., & Drickamer, M. A. 1998, "Older persons' preferences for site of treatment in acute illness", *Journal of General Internal Medicine*, vol. 13, no. 8, pp. 522-527.	1998	1126
Fried, T. R., Van Doorn, C., O'Leary, J. R., Tinetti, M. E., & Drickamer, M. A. 2000, "Older persons' preferences for home vs hospital care in the treatment of acute illness", *Archives of Internal Medicine*, vol. 160, no. 10, pp. 1501-1506.	2000	1127
Gravil, J. H., Al Rawas, O. A., Cotton, M. M., Flanigan, U., Irwin, A., & Stevenson, R. D. 1998, "Home	1998	19

treatment of exacerbations of chronic obstructive pulmonary disease by an acute respiratory assessment service", *Lancet*, vol. 351, no. 9119, pp. 1853-1855.		
Skwarska, E., Cohen, G., Skwarski, K. M., Lamb, C., Bushell, D., Parker, S., & MacNee, W. 2000, "Randomised controlled trial of supported discharge in patients with exacerbations of chronic obstructive pulmonary disease", *Thorax*, vol. 55, no. 11, pp. 907-912.	2000	221
Ojoo, J. C., Moon, T., McGlone, S., Martin, K., Gardiner, E. D., Greenstone, M. A., & Morice, A. H. 2002, "Patients' and carers' preferences in two models of care for acute exacerbations of COPD: results of a randomised controlled trial", *Thorax*, vol. 57, no. 2, pp. 167-169.	2002	1130
Hernandez, C., Casas, A., Escarrabill, J., Alonso, J., Puig-Junoy, J., Farrero, E., Vilagut, G., Collvinent, B., Rodriguez-Roisin, R., & Roca, J. 2003, "Home hospitalisation of exacerbated chronic obstructive pulmonary disease patients", *Eur Respir J*, vol. 21, no. 1, pp. 58-67.	2003	19475
Early discharge		
Author	**Publication Date**	**ID**
Cotton, M. M., Bucknall, C. E., Dagg, K. D., Johnson, M. K., MacGregor, G., Stewart, C., & Stevenson, R. D. 2000, "Early discharge for patients with exacerbations of chronic obstructive pulmonary disease: a	2000	220

randomised controlled trial", *Thorax*, vol. 55, no. 11, pp. 902-906.		

Author / Title / Reference / Yr	Davies, L., Wilkinson, M., Bonner, S., Calverley, P. M., & Angus, R. M. 2000, ""Hospital at home" versus hospital care in patients with exacerbations of chronic obstructive pulmonary disease: prospective randomised controlled trial", *BMJ*, vol. 321, pp. 1265-1268. Ref ID: 1059
N=	N=150 Duration=18 months study with three months follow-up Centres=University teaching hospital Geographic site=UK
Design	RCT
Aim	• To compare "hospital at home" and hospital care as an inpatient in acute exacerbations of COPD • Hypothesised that selected patients currently admitted with exacerbations of COPD could safely be cared for at home with sufficient support.
Operational Definition	Diagnosis of COPD based upon BTS criteria Exacerbation was defined as increased breathlessness and an increase in at least two of the following symptoms for 24 hrs or more; cough frequency or severity, sputum volume or purulence and wheeze.
Inclusion / Exclusion Criteria **See Q121**	**Inclusion criteria:** FEV1<80% predicted FEV1/FVC ratio <70% Mini mental state score >7 Pulse <100 bpm Systolic BP >100 mmHg PH >7.35 pO2>7.3 kPa pCO2 <8 kPa Total WBC 4-20x10^9/l **Exclusion criteria** Asthma Marked use of accessory muscles Suspected underlying malignancy Pneumothorax or pneumonia Uncontrolled LVF Acute changes on EEG Requirement for full time nursing care Requirement for IV therapy
Population	COPD exacerbations (asthmatics excluded).
Intervention **Q120**	Home care N=100 Hospital at home run from the accident and emergency department and not involving an overnight hospital stay. The Acute Chest Triage Rapid Intervention Team (ACTRITE) intercepted patients accepted for hospital admission with exacerbations of COPD in the A&E dept. A specialist nurse based in the A&E dept escorted Pts home. Pts GPs were informed of home care. Social support was immediately available if required. Nurses visited the pts mornings and evenings for 3 days and thereafter at the discretion of the nurses. Evening and night cover was provided with the agreement of pre-existing services by district nurses.
Comparison	Hospital care N=50
Outcome	Number of subsequent admissions to hospital during the first two wks of home care, the number of admissions to hospital in the 3/12 after this period, and changes in FEV1 after the use of bronchodilator. Health status in a subgroup of those randomised, health related quality of life (SGRQ) during the first wk of the exacerbation. Fifty of these completed a second

	such questionnaire at three months.
Characteristics	Mean age 70yrs, 50:50 male / female, 37% had started a course of high dose oral corticosteroids and 50% had started oral antibiotics within 2 or 3 days of randomisation. No difference was found between these pts and the others for FEV1 after the use of a bronchodilator, duration of hospital or home care, or distribution between the treatment arms.
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1b
Results	**FEV1** No significant differences were found in FEV1 after use of a bronchodilator at two wks or three months between the two groups. **Readmission** 37% home care group and 34% hospital care were readmitted at three months. **Mortality** No significant differences were found between the two groups at three months. **Subgroup analyses of HRQL** Data from repeat SGRQ were available in 50/90 pts at three months; 34 received home care and 16 received hospital care At three months there was no difference in the scores either from admission or between the groups.
ID	1059

Author / Title / Reference / Yr	Fried, T. R., Van Doorn, C., Tinetti, M. E., & Drickamer, M. A. 1998, "Older persons' preferences for site of treatment in acute illness", *Journal of General Internal Medicine*, vol. 13, no. 8, pp. 522-527. Ref ID: 1126
N=	N=29. Geographical site=USA
Design	Qualitative research
Methodology	Grounded theory
Method / Research Tool	Sample size – number of participants interviewed continued until data saturation achieved. In-depth open-ended interviews. Interviews lasted 30-60 minutes and were taped and transcribed.
Data analysis	Constant comparative method was used. Segments of the transcripts were initially coded into discrete themes by each of the investigators independently. A qualitative research software program facilitated assignment of codes to text. Themes and concepts were developed from the qualitative data by two researchers and an inter-rater reliability framework was agreed.
Aim	To elicit how older persons form preferences for site of medical care by examining their perceptions of home and hospital care.
Population	Older persons' hospitalised (1 to 6 months earlier) with congestive heart failure, chronic obstructive pulmonary disease or pneumonia and were receiving home care services
Characteristics	Age range 65 to 89 yrs / 21 (72%) female / 18 (62%) white / 17 (59%) lived alone.

	All participants had been hospitalised with their illness episode and none had been given a choice about treatment site.
Results	**Perception of services available at home** Encouraged respondents to consider the possibility of a wide variety of home care services; many simply could not imagine receiving the services necessary to meet their needs. Concerns were focused upon the American system of cost of payment, provision of only limited services (which arose from home care as a supportive service rather than as an integral part of their treatment) and inability of the nurse to take any action apart from refer problems to a doctor. **Importance of outcome over process of care** Preference for site of care depended on the anticipated outcome of the illness episode. The likelihood of surviving the illness was the most important determinant of preference for home or hospital. Home care was seen for some as a low intensity service. **Preference for care at home and in the hospital** 15 (52%) preferred home care because of positive aspects of the comfort of home e.g. sleep better, confined in hospital, not being surrounded by other sick people, receiving the undivided attention of the nurse during a home visit. For those who preferred the hospital, the sense of safety, closer monitoring, availability of help at night (both emotional and physical support) and less burden placed upon families were cited. **Factors influencing perceptions** Because perceptions of home and hospital differed researchers sought to understand the factors influencing respondents' perceptions. Four factors were elicited; social support, religiousness, self-reliance and past experience with illness. Previous experiences with illness and its symptoms influenced preference for site of care, *"I don't think my kids would know what to do. I might make them nervous…..I couldn't catch my breath, you know, and then you don't want them to leave. You're afraid".*
SIGN Quality Rating	No SIGN Checklist available for qualitative methodologies. Critical Appraisal Skills programme (CASP) checklist for qualitative research used. Equates to "+"
Hierarchy of Evidence Grading	III
ID	1126

Author / Title / Reference / Yr	Fried, T. R., Van Doorn, C., O'Leary, J. R., Tinetti, M. E., & Drickamer, M. A. 2000, "Older persons' preferences for home vs hospital care in the treatment of acute illness", *Archives of Internal Medicine*, vol. 160, no. 10, pp. 1501-1506. Ref ID: 1127
N=	N=246. Time period July 1997-Jan 1998. Geographic location=USA. Site=2 urban teaching hospitals.
Design	Survey
Method / Research Tool	Participants were interviewed by telephone 2/12 after hospitalisation. Participants were asked to indicate their preference for home or hospital as site of care based upon a scenario (derived from previous qualitative research (ID 1126). The scenario was described as 1) home and hospital provide an equal likelihood of survival 2) the same treatments, such as IV medications, O2, blood tests and XR would be available in the home and in the hospital and 3) a daily nursing visit and several hrs of home health aide assistance would be provided at no cost to the patient. All participants were then asked to choose from a list of the most important reasons underlying their preference. The scenario was then changed according to differing variables and participants were then asked whether this resulted in a change in preference.
Aim	Purpose of the study was to describe preferences for treatment site among older persons with conditions identified as potentially amenable to treatment in both the home and the hospital.
Population	Older persons' with pneumonia, congestive heart failure, and exacerbation of COPD
Characteristics	Mean age 76yrs / gender 57% female / 92% white / 37% live alone / 26% diagnosis of COPD.
Results	If home and hospital offered equivalent outcomes, 46% of the sample preferred treatment at home. Preferences were heavily dependent on the outcome of the illness, physician opinion about the best site of care and the provision of home visits. Higher education, white race, living with a spouse and having 2 or more dependencies in activities of daily living were associated with home care.
SIGN Quality Rating	No SIGN Checklist available for survey. Critical Appraisal Skills programme (CASP) checklist for qualitative research used. Equates to "+" but limited results.
Hierarchy of Evidence Grading	III
ID	1127

Author / Title / Reference / Yr	Gravil, J. H., Al Rawas, O. A., Cotton, M. M., Flanigan, U., Irwin, A., & Stevenson, R. D. 1998, "Home treatment of exacerbations of chronic obstructive pulmonary disease by an acute respiratory assessment service", *Lancet*, vol. 351, no. 9119, pp. 1853-1855. Ref ID: 19
N=	N=962 pts over 3-5 years (Time period Dec 1993 to June 1997)
Design	Service Evaluation

Aim	Assessed pts with exacerbation of COPD after referral to a hospital respiratory dept by their family physicians.
Operational Definition	Severe exacerbations: Respiratory rate of >25bpm, heart rate of >110bpm, partial pressure of O_2 <8.0kPa and abnormal CXR.
Population	Pts with exacerbations of COPD. Severe disease with a mean FEV1 of 1.02 L
Service provision **Q120 / Q121**	Options: 1. Doctor admitted pts to hospital. 2. Doctor sends pt home for treatment with respiratory-nurse supervision • Baseline assessment: CXR, oxygen saturation, arterial gas analysis, spirometry and physical assessment. • Decision to admit: Made by degree of disability or frailty, the degree of support in the community (lived alone), severity of exacerbation, mental state, or the presence of a coexisting disorder that required admission. • Severity of the exacerbation: Assessed by clinical signs of respiratory distress, XR and arterial gases. • Suitable pts were allowed home with an individualised package of care. • A respiratory nurse visited each pt daily between 09:00 and 12:00 and assessed progress clinically and with spirometry and O_2 saturation.
Outcome	• 145 (15%) pts admitted. 6% of pts with uncomplicated COPD and 6% with additional medical disorders were admitted to hospital at assessment. • 768 (80%) pts treated at home and of these 115 (12% of all pts) required admission during follow-up. None of the referred pts had uncompensated respiratory acidosis. • 49 (5%) of 962 were inappropriate referrals • One pt died at home. • Severity of exacerbations was similar among pts treated at home and those who later required admission. • FEV1 (L) admitted at assessment 1.05 (0.63) / treated at home 1.02 (0.53) • Patient satisfaction questionnaire showed that 80% of pts would be happy to be treated at home and 14% would prefer to be admitted to hospital. • Of pts treated successfully at home, 53% compared with 88% of those admitted at assessment fulfilled at least one inclusion criterion for a severe acute exacerbation. There was little difference in initial severity of exacerbation between those treated successfully at home and those admitted during follow up (development of additional disorders).
Characteristics	Mean age 65yrs (range 27-94) / lived alone 29% / Mean (SD) FEV1 (L) 1.02 (0.5) / Mean (SD) SGRQ score 72 (18.6)
SIGN Quality Rating	Not critically appraised. Service evaluation
Hierarchy of Evidence Grading	Not within hierarchy of evidence Service Evaluation
ID	19

Author / Title / Reference / Yr	Skwarska, E., Cohen, G., Skwarski, K. M., Lamb, C., Bushell, D., Parker, S., & MacNee, W. 2000, "Randomised controlled trial of supported discharge in patients with exacerbations of chronic obstructive pulmonary disease", *Thorax*, vol. 55, no. 11

	pp. 907-912. Ref ID: 221
N=	N=184 Duration=18 months Centres=Royal Infirmary Geographic site= Scotland
Design	RCT
Aim	To compare outcomes in those managed at home with support with those admitted to hospital.
Operational Definition	Assessed with respect to 13 indicators of severity of the exacerbation, as per the BTS guidelines
Inclusion / Exclusion Criteria See Q121	**Exclusion criteria** Impaired consciousness, acute confusion, acute changes on X-ray or an arterial pH of <7.3.
Population	COPD exacerbations
Intervention Q120	Home care N=122 • All patients were seen initially by the staff in A&E or by the medical registrar on call • The Acute Respiratory Assessment Service (ARAS) was available on weekdays from 09:00 to 17:00. Pts presenting overnight (after 17:00 hrs) were assessed the following morning in the admissions unit • Pts were visited at home by an ARAS nurse the following day and thereafter at intervals of 2-3 days to monitor the need for treatment. The progress of the pts was assessed in consultation with the two ARAS nurses weekly at a review meeting by the consultant in charge of the trial. Medical advice was available daily from the on call respiratory team. GP was aware of follow up by the ARAS team. Any additional care they had received from GP / social services or informal carers are reported as outcome measures.
Comparison	Hospital care N=62
Outcomes	Follow-up and readmission rates, respiratory function, CRQ, satisfaction with service, additional care, and mean health service cost per pt.
Characteristics	Mean age 69yrs range 39-86 / sex % female 53% / Current smoker 39% Mean resp rate 23 / mean peak exp flow l/min 168 / Mean FEV1 0.74 / Mean O2 saturation 92%
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1b
Results	**Follow up and readmission** 7% of those supported at home were admitted to hospital for respiratory related problems before they were discharged from home care. For those discharged at the end of the exacerbation there were no significant differences in readmissions at 8 wks between the two groups. Among those discharged at the end of the exacerbation 25% of the home support group and 34% of the hospital admitted group were readmitted before the final assessment at 8wks (non significant difference). The median time to discharge was 7 days for the home group and 5 days for the hospital group ($p<0.01$). **Respiratory Function**

	Between discharge and the final assessment at 8wks, measurements of respiratory function did not change significantly except for an increase in O2 saturation of 2.4% in the hospital group. **Chronic Respiratory Questionnaire (CRQ)** There were no significant differences between the groups when measured at 8wks. **Satisfaction with service** 69% pts treated at home completed satisfaction questionnaire, 95% of these said that they were “completely satisfied”. No comparison data given for hospital group. 50% GPs replied. 65% felt that there was no increase in demand on their practice with those pts managed at home. 33% reported decreased demands and 2% reported increased demands. **Additional support services** Home support pts received an average of 3.8 visits at home from the ARAS nurses before being discharged. Attendance by GPs and carers did not differ significantly between the groups during the 8wk follow up period. **Mean health service cost per pt** £877 for home support group £1753 for pts admitted to hospital. The mean cost of GP care between discharge and final assessment was slightly greater for the hospitalised pts than for the home pts.
ID	221

Author / Title / Reference / Yr	Ojoo, J. C., Moon, T., McGlone, S., Martin, K., Gardiner, E. D., Greenstone, M. A., & Morice, A. H. 2002, "Patients' and carers' preferences in two models of care for acute exacerbations of COPD: results of a randomised controlled trial", *Thorax*, vol. 57, no. 2, pp. 167-169. Ref ID: 1130
N=	N=60 Duration=9/12 Centres=Medical Chest Unit of a University Hospital Geographic site=UK
Design	RCT
Aim	To ascertain the acceptability to pts and carers of Hospital at Home (HaH) schemes compared to in-patient care.
Operational Definition	FEV1 / FVC ratio of <70%. FEV1 reversibility to salbutamol <15% (obtained on a previous admission or clinic visit). Exacerbation was defined as worsening of symptoms with any combination of increased sputum purulence and / or volume, and worsening dyspnoea.
Population	COPD acute exacerbation
Intervention	Home care N=30
Comparison	Hospital care N=30
Outcome	See factors listed in results section
Characteristics	Average age 70yrs / 50% Men / Mean [SD] admission FEV1 0.85 [0.34] conventional arm, 1.0 [0.38] domiciliary arm / Mean

	[SD] symptoms score on admission (%) 63.6 (17.8) conventional arm, 63.0 (13) domiciliary arm. Mean [SD] total SGRQ score 67.6 [16.3] conventional arm, 67.9 [10.7] domiciliary arm. Excluded if had complications with the exacerbation; acidosis, cor pulmonale, and acute changes on CXR.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
Results	There were **no significant differences between the two groups** for the following outcomes: • Mean improvement in FEV1, mean improvement in FVC, mean improvement in symptom score, mean no of days in care, mean no of readmissions per pt at 3/12, readmission rate at 3/12 and number of deaths at 3/12. **Preferences** • 60% in the conventional arm and 96% in the domiciliary arm would have preferred domiciliary management. • 34 carers completed the questionnaires and respective carer preference figures were 6/14 (43%) and 17/20 (86%) • The pts and carers in the Hospital at Home arm were significantly more likely than those in the conventional arm to prefer domiciliary care (p=0.001 and p=0.01 respectively). **Satisfaction** There were no significant differences in the satisfaction scores with the care package for either patient or carers. There was no association between preferred site of management and age or sex of pt, treatment with maintenance steroids, home nebuliser or oxygen, frequency of admissions in the preceding yr, symptom score at admission and whether the pt lived alone or had a partner.
NCC CC ID	1130

Author / Title / Reference / Yr	Hernandez, C., Casas, A., Escarrabill, J., Alonso, J., Puig-Junoy, J., Farrero, E., Vilagut, G., Collvinent, B., Rodriguez-Roisin, R., & Roca, J. 2003, "Home hospitalisation of exacerbated chronic obstructive pulmonary disease patients", *Eur Respir J*, vol. 21, no. 1, pp. 58-67.
N=	N=222, Duration = 8/52, Emergency Room of two tertiary hospitals, location = Spain
Design	RCT
Aim	It was postulated that home hospitalisation with free patient phone access to a specialised nurse should generate a better outcome at lower direct costs than inpatient hospitalisation.
Operational Definition	COPD exacerbation as a major cause of referral to the ER, and absence of any criteria for imperative hospitalisation as stated by the British Thoracic Society (BTS) guidelines
Population	COPD acute exacerbation
Intervention	N=121. The HH intervention had three main objectives: 1) an immediate or early discharge from the hospital was encouraged by the

	specialised team aiming to either avoid or reduce the length of inpatient hospitalisation; 2) a comprehensive therapeutic approach was tailored on an individual basis, according to the needs detected by the specialised team; and 3) patient support by a skilled respiratory nurse either through home visits or free-phone consultation was ensured during the 8-week follow-up period. A maximum of five nurse visits at home were permitted during the 8-week follow-up period, but patient's phone calls to the nurse were not limited in number. Full details of intervention were appended to the study report
Comparison	N=101 Patients included in the conventional care group (controls) were evaluated by the attending physician at the ER who decided either on inpatient hospital admission or discharge.
Outcome	Readmission rates, and lengths were recorded over the 8 week follow up period, and number of emergency room visits recorded. HRQL outcomes were assessed as were satisfaction with care. HRQL status during the previous year (St George's Respiratory Questionnaire (SGRQ) and Short-Form 12-item survey (SF-12), both validated scales, were employed. At 8-week follow-up period, the same questionnaires were used. Also forced spirometry, chest radiograph films and arterial blood gases were also obtained.
Characteristics	Average age 70.8yrs / 96.8% Male / Dyspnoea score (VAS) 6.2 [SD] 3.2 / % requiring admission for exacerbatiosn in previous yr 40.7% / pH 7.4 [SD] 0.2 / PaCO2 43.2 [SD] 8.2. FEV1 at end of study = 42% % predicted
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
Results	**Readmission rates** The rate of hospital readmissions during this period was ~ 25%, with no differences between groups. **ER visits** In the control group, however, the rate of relapses requiring new ER admission without subsequent hospital readmissions almost doubled the figure shown by the HH patients ($p<0.05$) being 0.31 ±0.62 and 0.13±0.43 respectively **Mortality** No significant difference **SGRQ** Hospital at home =-6.9, conventional care =-2.4 ($p=0.05$) **Patient satisfaction score** Hospital at home =8.0, conventional care =7.5 ($p=0.03$) **Knowledge of care** A higher percentage of patients in the HH group had a substantial improvement in knowledge of the disease (HH 58% versus 27% for controls, ($p<0.01$).
NCC CC ID	Ref ID: 19475

Author / Title / Reference / Yr	Cotton, M. M., Bucknall, C. E., Dagg, K. D., Johnson, M. K., MacGregor, G., Stewart, C., & Stevenson, R. D. 2000, "Early discharge for patients with exacerbations of chronic obstructive pulmonary disease: a randomised controlled trial", *Thorax*, vol. 55, no. 11, pp. 902-906. Ref ID: 220
N=	N=81 Duration=Study recruitment 14 months follow up 60 days. Centres=Large University Teaching Hospital. Geographic site=Scotland
Design	RCT
Aim	• Compare conventional inpatient management of patients with an acute exacerbation of COPD with a policy of early discharge followed by domiciliary respiratory nurse support. • Hypothesised that patients currently treated throughout the course of their illness in hospital could be successfully treated at home after a brief period as inpatients.
Operational Definition	Operational definition of COPD not given.
Inclusion / Exclusion Criteria See Q121	**Exclusions:** Not resident in Glasgow, homeless, unable to give informed consent, did not have access to a telephone, requiring inpatient management or investigation for medical problems, life threatening respiratory failure defined by an acidosis (H^+ >45nM).
Population	COPD exacerbation ("A patient was considered to have an exacerbation of COPD if this formed part of the clinical differential diagnosis of the admitting medical unit")
Intervention Q120	N=41 Early discharge group Pts were sent home on the next working day after recruitment, ideally within three days of admission. Patients were visited by a respiratory nurse on the first morning after discharge and thereafter at intervals determined by the nurse. The respiratory nurse in the early discharge group could adjust treatment at home after discussion with a member of the respiratory medical staff. "Home management followed the practice developed for Acute Respiratory Assessment Service (ARAS) for pts referred by their family physicians with exacerbations of COPD". See ID 19. Patient discharge was not supported by increased use of social services support of rehabilitation services such as physiotherapy. Pre-existing social services support was reinstated if stopped before discharge.
Comparison	N=40 Hospital inpatient care
Outcomes	• Rate of readmission and consequent additional number of days spent in hospital during the 60 days following initial admission. • Deaths during the same period.

Characteristics	(SE) Hospital group / Early discharge group Average age: 68yrs 66yrs Women: 60% 54% FEV1 (l) 0.94 (0.06) 0.95 (0.08) FEV1 (% pred) 44 (3) 41 (3) FEV1 / FVC (5) 46 (2) 45 (2)
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1b
Results	On an intention to treat basis, a policy of early discharge reduced in patient stay from a mean of 6.1 (range 1-13) days with conventional management to 3.2 (1-16) days with an early discharge policy. There were no significant differences in the: • Number of patients that were readmitted in each group was identical at 30%. • Number of additional days readmitted patients spent in hospital Number of deaths
ID	220

COPD Evidence Tables

The evidence tables are presented in section order.

The methodological quality of each paper was rated using the Scottish Intercollegiate Guidelines Network (SIGN) system (Scottish Intercollegiate Guidelines Network. SIGN 50 Guideline Developers Handbook, 2001; ID 19457):

++	All or most of the SIGN methodology checklist criteria were fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
+	Some of the criteria were fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
-	Few or no criteria were fulfilled. The conclusions of the study are thought likely or very likely to alter.

Chronic Obstructive Pulmonary Disease: Management of adults with Chronic Obstructive Pulmonary Disease in Primary and Secondary Care

Management of exacerbations of COPD
Systemic steroids
Index

Author	Publication Date	ID
Wood-Baker R, Walters EH, Gibson P. Oral corticosteroids for acute exacerbations of chronic obstructive pulmonary disease (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2003. Oxford: Update Software.	2003	1364
Maltais, F., Ostinelli, J., Bourbeau, J., Tonnel, A. B., Jacquemet, N., Haddon, J., Rouleau, M., Boukhana, M., Benoit, M. J., & Duroux, P. 2002, "Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: A randomized controlled trial", *American Journal of Respiratory & Critical Care Medicine*, vol. 165, no. 5, pp. 698-703.	2002	1362
Singh, J. M., Palda, V. A., Stanbrook, M. B., & Chapman, K. R. 2002, "Corticosteroid therapy for pts with acute exacerbations of COPD: a systematic review.", *Archives of Internal Medicine*, vol. 162, no. 22, pp. 2527-2536.	2002	1484
McCrory, D. C., Brown, C., Gray, R. N., Goslin, R. E., MacIntyre, N. R., Kolimaga, J. T., Oddone, E. Z., & Matchar, D. 2001, *Management of acute exacerbations of chronic obstructive pulmonary disease.*, Agency for Healthcare Research and	2001	1145

Quality., Rockville, MD, USA, 256.		
Davies, L., Angus, R. M., & Calverley, P. M. A. 1999, "Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial", *Lancet*, vol. 354, no. 9177, pp. 456-460.	1999	217
Niewoehner, D. E., Erbland, M. L., Deupree, R. H., Collins, D., Gross, N. J., Light, R. W., Anderson, P., & Morgan, M. A. 1999, "Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease", *New England Journal of Medicine*, vol. 340, no. 25, pp. 1941-1947.	1999	36
Bullard, M. J., Liaw, S. J., Tsai, Y. H., & Min, H. P. 1996, "Early corticosteroid use in acute exacerbations of chronic airflow obstruction.[comment]", *American Journal of Emergency Medicine.*, vol. 14, no. 2, pp. 139-143.	1996	1360

Author / Title / Reference / Yr	Wood-Baker R, Walters EH, Gibson P. Oral corticosteroids for acute exacerbations of chronic obstructive pulmonary disease (Cochrane Review). *The Cochrane Library.Oxford: Update Software* 2003;**Issue 3**.
N=	N =692. International trials. N=8 RCTs, Various durations.
Research Design	Systematic review with meta-analysis
Aim	A review to determine the effect of corticosteroids on the outcome of patients with acute exacerbations of COPD
Operational Definition	COPD definition not stated
Population	COPD patients with a recent functional deterioration
Intervention	Interventions of corticosteroids given orally or parentally, with a variety of drugs, at a range of doses and for varying periods of time
Comparison	Appropriate placebo control
Outcome	A variety of outcome measures are reported from lung function measurements, arterial blood gas measurements, to symptom scores QOL indices, hospitalisation, mortality and adverse drug effects. All to various time points
Characteristics	Populations varied in terms of definition of acute exacerbation between trials, mean age range 61yrs – 72yrs, predominantly male
Results	**FEV1 at up to 72 hours** This out come was reported in 6 trials with an overall weighed mean difference of 120ml (95% CI 5ml to 190ml) in favour of the use of steroids over placebo (fixed effect model) with no heterogeneity found. This included the study by Ballard et al in which the data presented in the original trial report was inappropriately reported, if this study was removed from the analysis (with the data used) the effect would have remained significant as the study only provided 7.7% of the weight to the analysis and the difference in means in this study was less marked than the overall mean produced. **FVC up to 27 hours** 3 studies reported this outcome the pooled weighted mean difference did not detect a significant difference between intervention and control arms **Later spirometric endpoints** after 72 hours The analysis of 4 trial reporting on FEV1 at time points later then 72 hours showed no significant difference between treatment regimes, similarly the 2 trials that reported on FVC at later time points also found no significant difference in group means when pooled. **Duration of hospital stay** Analysis of length of stay way not possible owing to skewed distribution of results in 2 of the 3 trials that reported this outcome, as standard deviations of group means could not be established. **Treatment failure** The pooled results of the 5 studies that detailed treatment failure showed a significant beneficial treatment effect of steroids over placebo with a combined OR of 0.50 (95% CI 0.32 to 0.79) using the Peto odds ratio. However this analysis pointed to significant heterogeneity between the studies (p=0.0071 for the chi squared test) which may be due to the wide variation in definitions of treatment failure used in the various studies **QOL** Only 2 of the studies reviewed gave analysis of the effect of corticosteroids on quality of life, but as these were assessed using different analogue scales the quantitative analysis of these is going to be difficult to comprehend **Exercise capacity** Only one trial (Wood-Baker et al) provided date on distance walked in 6 minutes, this found no significant differences between groups treated with corticosteroids or placebo

	Adverse drug reactions Of the 6 studies that reported side effects 3 of these documented no occurrences in the placebo group and therefore the treatment effect was not estimable. Amongst the other three, the pooled odds ratio for risk of having an adverse effect with treatment suggested that patients on steroids have odds 2.7 times more likely than those on placebo OR 2.70 (95% CI 1.72 to 4.23) using the Peto odds ratio. This analysis showed no heterogeneity, although with only 3 trials included the statistical power of the test to detect this was low. **Mortality** An analysis of 5 studies (where at least one event was reported in each of the study arms) found no significant difference between the odds of mortality between patients on corticosteroids or placebo
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1a
NCC CC ID	1364
Studies included	Albert (1980), Bullard (1996), Davies (1999), Emerman (1989), Niewoehner (1999), Rostom (1994), Thompson (1996), Wood-Baker (1997).

Author / Title / Reference / Yr	Maltais, F., Ostinelli, J., Bourbeau, J., Tonnel, A. B., Jacquemet, N., Haddon, J., Rouleau, M., Boukhana, M., Benoit, M. J., & Duroux, P. 2002, "Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: A randomized controlled trial", *American Journal of Respiratory & Critical Care Medicine*, vol. 165, no. 5, pp. 698-703. Ref ID: 1362
N=	N=199, Belgium, Canada and France,34 sites, follow up to 10 days
Research Design	RCT
Aim	A study to evaluate the efficacy and safety of nebulised budesonide in comparison to oral prednisolone and placebo to treat exacerbations of COPD requiring hospitalisation
Operational Definition	COPD defined on clinical evaluation to ATS criteria
Population	COPD patient admitted to hospital with acute exacerbations
Intervention	N=71 BUD group received nebulised budesonide at 2 mg every 6 hours for 72hrs, then 2000 µg/d up to 10 day 10, with placebo tablets, N=62 PRED group received 30mg prednisolone orally every 12 hours to 3 days then at 40mg/day up to day 10 with placebo nebuliser, the
Comparison	N=66 Placebo group received placebo nebuliser and tablets to day 10
Outcome	Primary endpoints were lung function tests to post-bronchodilator FEV1 to day 3, with secondary endpoints pre-bronchodilator FEV1, dyspnoea score and arterial blood gases to day 3, with duration of hospitalisation and reported adverse events to day 10. COPD deterioration was also reported
Characteristics	Age =70yrs, Male =81%, FEV1 pre bronchodilator +0.82l, post bronchodilator =0.92l, pH =7.41, smoking =56 pack

	years
Results	Lung function over 3 days there were significant improvements in post-bronchodilator FEV1 in both BUD group 0.1l (95% CI 0.92 l to 0.18 l) and PRED group 0.16 l (0.09 l to 0.24 l) compared to placebo treated patients. There was no significant differences between the BUD and PRED groups. Also there was a faster rate of improvement in FEV1 in both groups compared with placebo. However there was only an significant difference to 3 days in pre-bronchodilator FEV1 between patients taking PRED and placebo at 0.12l (0.03 l to 0.21 l) Clinical outcomes The reduction in dyspnoea on the Borg scale showed comparable changes in all three groups. The occurrence of COPD deterioration to 3 days was not significantly different amongst the treatment arms. Arterial blood gasses - There was a significant improvement in arterial PaO2 to 3 days amongst patients treated with PRED (7mmHg) compared to placebo (4 mmHg) ($p<0.05$) with no significant difference between the BUD and placebo groups. In contrast the decline in PaCO2 was significantly greater in both active groups than with placebo ($p<0.05$ for both active groups Vs placebo). Hospitalisation 42 % of the patients in the BUD group, 35% in the PRED group and 48% in the placebo group were still hospitalised to day 10 following admission, with no significant differences between groups. Similarly the median length of hospitalisation at 7, 6, and 8 days respectively was not significantly different. Adverse events The overall rate of adverse events was not significantly different between the study arms. However a greater proportion of the patients developed hyperglycaemia in the PRED group (n=7) than in the BUD group (n=1) and the placebo group (n=0).
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1a
NCC CC ID	1362

Author / Title / Reference / Yr	Singh, J. M., Palda, V. A., Stanbrook, M. B., & Chapman, K. R. 2002, "Corticosteroid therapy for pts with acute exacerbations of COPD: a systematic review.", *Archives of Internal Medicine*, vol. 162, no. 22, pp. 2527-2536. Ref ID: 1484
N=	N= 478, International studies, 8 RCTs, various durations
Research Design	Systematic review
Aim	A review to determine whether systemic corticosteroids are of benefit to people with acute exacerbations of COPD
Operational Definition	Definition of COPD and exacerbation may have varied between studies
Population	Studies of the use of systemic corticosteroids in patients with COPD exacerbations
Intervention	A range of systemic corticosteroids interventions with two studies with IV administration, three studies with oral treatment and 3 studies with a combination of both, at a range of doses

Comparison	All studies with placebo control
Outcome	Spirometric measures were the most widely reported with FEV1 as a surrogate marker of clinical outcome, other outcomes identified included health care measures including two trials where treatment failure was noted and three trials where length of hospitalisation was analysed. Adverse events in corticosteroid therapy was assessed by a separate search
Characteristics	All inpatients (including emergency department patients) . Age, gender, and clinical status not stated
Results	**Spirometric studies** 1 large trial by Niewoehner et al showed a benefit in terms of FEV1 with a maximal difference of 0.12l in favour of corticosteroid use after 1 day persisting to 3 days, but with no significant difference found after 2 weeks. Another good quality trial by Davies et al showed the rate of change of post-bronchodilator FEV1 in patients in the corticosteroid arm to be 3 times that of patients in the placebo group, this effect did not last beyond the reference hospitalisation; this despite an increased drop out of more sick patients in the control arm. Thompson et al produced a study in outpatient management of exacerbations with moderate airflow obstruction where patients given corticosteroids had a faster recovery of FEV1 and had a greater FEV1 at 10 days than patients given placebo. In a small trial of patients with severe airways obstruction patients treated with IV steroids conducted by Albert and colleagues steroid treated patients had a significant improvement in FEV1 over placebo treated patients to 3 days. The study by Bullard et al that did not explicitly exclude Asthma patients found that at 6 hours patients benefited with corticosteroid treatment with significant improvements in spirometric indexes. In contrast three other studies, by Emerman et al, Rostom et al, and Wood-Baker et al all failed to show beneficial effects of steroids in lung function parameters, but this may be attributable to a short outcome measurement time, lack of power, and excessive withdrawals due to protocol violations respectively. **Health Care outcomes** Not all studies reported in these outcomes. As a composite end point of treatment failure as death / intubation / additional concomitant therapy / readmission after discharge Niewoehner et al found patients treated with steroids had a significant decrease in this measure compared to those receiving placebo. Thompson et al in a small study of outpatients found that half of the placebo treated group required admission and open label steroid therapy while there were no admissions amongst the steroid intervention arm. 3 studies reported outcomes on hospital length of stay, Niewoehner et al reported a small reduction in the length of stay of steroid treated patients 1.2 days less than that of control patients, Davies and colleagues similarly found shorter stays for corticosteroid treated patients (7days) compared to those treated with placebo (9days), a statistically significant difference. There was no significant difference in hospital length of stay recorded in a study by Wood-Baker et al, however the author states that there may have been insufficient power to detect a difference in this outcome. **Adverse events** Owing to the lack of consistency of reporting risks of therapy amongst the trials included a separate search was undertaken in this area. There are no prospective studies of long-term effects of corticosteroids in COPD patients with disease-matched controls in terms of risk of osteoporosis. Three of the reviewed trials (Niewoehner et al, Davies et al, and Albert et al) found that patients treated with steroids more commonly developed hyperglycaemia or glycosuria than control patients. The only evidence for an increase in serious infections in COPD receiving steroids is a post hoc analysis in the Niewoehner et al trial suggesting a higher rate in patients on a 8 week course than those on a 2 week course or placebo, however this difference was not statistically significant

SIGN Quality Rating	+
Hierarchy of Evidence Grading	1a
NCC CC ID	1484
Studies included	Albert (1980), Bullard (1996), Davies (1999), Emerman (1989), Niewoehner (1999), Rostom (1994), Thompson (1996), Wood-Baker (1997).

Author / Title / Reference / Yr	McCrory, D. C., Brown, C., Gray, R. N., Goslin, R. E., MacIntyre, N. R., Kolimaga, J. T., Oddone, E. Z., & Matchar, D. 2001, *Management of acute exacerbations of chronic obstructive pulmonary disease.*, Agency for Healthcare Research and Quality., Rockville, MD, USA, 256. Ref ID: 1145
N=	N=6 RCTs
Design	Systematic Review / Technology Assessment
Aim	To assess the efficacy and side effects of corticosteroids
Population	Acute exacerbations of COPD
Intervention and Comparisons	The trials varied in many respects: dosage and duration of corticosteroid treatment, route of administration (oral or IV), duration of observation, and treatment setting. (Bullard, Liaw, Tsai, et al., 1996; Emerman, Connors, Lukens, et al., 1989b) - Conducted in Emergency Dept and considered only short-term (less than 6 hours) outcomes . (Albert, Martin, and Lewis, 1980; Niewoehner, Erbland, Deupree, et al., 1999), and one used oral prednisolone (Davies, Angus, and Calverley, 1999). - Were conducted on inpatients and measured outcomes over several days to weeks; two of these studies used IV-administered corticosteroids (Thompson, Nielson, Carvalho, et al., 1996) - Was unique in including pre enrolled patients with COPD who had initiated steroid treatment for acute exacerbations as outpatients; this trial also enrolled other patients through the ED. (Albert, Martin, and Lewis, 1980; Niewoehner, Erbland, Deupree, et al., 1999; Thompson, Nielson, Carvalho, et al., 1996) - Were performed in U.S. Department of Veterans Affairs Medical Centers
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1a
Results	Direct cut and paste from the document:

"The SCCOPE trial, a large multicenter study"…….."was designed to compare treatment failure (death, intubation, readmission, or intensification of drug treatment) rates between patients who did and did not receive systemic corticosteroids (Niewoehner, Erbland, Deupree, et al., 1999). Patients who were admitted for an acute exacerbation of COPD"……."assigned to receive 3 days of IV methylprednisolone or placebo. The IV steroids were followed by oral prednisone in a tapering dose over 12 days or 8 weeks"……."There were no important differences in any efficacy outcomes or adverse effects between the two groups; for most analyses reported, the two groups were combined. For the combined corticosteroid group, the risk of treatment failure was reduced by 10 percent, and FEV_1 showed an improvement averaging about 0.1 L in the first 3 days of treatment. No differences were observed in length of hospitalization or mortality. The improvement in FEV_1 observed in this trial is remarkably similar to the magnitude of benefit reported in several previous small trials, thus reinforcing the generalizability of this finding to different settings, populations, and dosages.

The ATS suggests that a difference of 13 percent in FEV_1, developing over a short period, is clinically important (American Thoracic Society, 1991"……."the magnitude of improvement in FEV_1 that is attributable to systemic corticosteroid observed in the SCCOPE trial appears to be clinically important".

"Differences in the dose and potency of the corticosteroid agents that were used account for a large variation in exposure in the included trials. The least intensive treatment that was administered was a single dose of hydrocortisone (100 mg IV), which is equivalent to 20 mg methylprednisolone (Bullard, Liaw, Tsai, et al., 1996). The most intensive regimen involved 125 mg of methylprednisolone IV, every 6 hours for 3 days, followed by an oral prednisone taper (Niewoehner, Erbland, Deupree, et al., 1999".

"Several trials have examined the time course of improvement in FEV_1 during treatment with systemic corticosteroids. The two trials that considered short-term outcomes of ED treatment failed to find significant differences in FEV_1 between corticosteroid- and placebo-treated patients (Bullard, Liaw, Tsai, et al., 1996; Emerman, Connors, Lukens, et al., 1989b) . However, trials that measured FEV_1 changes over a longer period of time did show significant differences. One trial measured FEV_1 improvement at only one time point (72 hours) and found a statistically significant improvement in patients treated with methylprednisolone (Albert, Martin, and Lewis, 1980). Other trials measured FEV_1 at multiple time points over longer time frames and found that most of the improvement occurs in the first 3–5 days of corticosteroid treatment (Davies, Angus, and Calverley, 1999; Niewoehner, Erbland, Deupree, et al., 1999; Thompson, Nielson, Carvalho, et al., 1996). Thompson, Nielson, Carvalho, et al. (1996) measured FEV_1 at days 3 and 10; while there was a trend toward better FEV_1 improvement in the steroid-treated group at day 3, this effect was significant at day 10, and the mean slope was significantly better. Davies, Angus, and Calverley (1999), measuring FEV_1 daily, found that by day 5, patients in the steroid-treated group had increased postbronchodilator FEV_1 to 92 percent of discharge values compared with 85 percent in the placebo-treated group ($p < 0.04$). In the SCCOPE trial, the difference in FEV_1 between corticosteroid- and placebo-treated patients was highest after the first day of treatment,

	remained statistically significant after the second and third days, and was no longer significant at 2 weeks". ***"Adverse Effects*** The most common adverse effect that was associated with systemic corticosteroids for acute exacerbation of COPD was hyperglycemia, which was reported in each of the three trials that provided data on adverse effects". ***"Summary*** *Several RCTs provide good evidence for a benefit from a short course of systemic corticosteroids in patients with acute exacerbation of COPD who require hospitalization. The SCCOPE trial included a randomized comparison between a 2- and 8-week course of systemic corticosteroids. Based on the finding that these courses were not importantly different in clinical outcome, the investigators concluded that the shorter course, which reduced adverse effects, is preferred. The optimal dose and duration of treatment remain uncertain, however, because small studies suggest that even lower doses (Davies, Angus, and Calverley, 1999) and even shorter courses of treatment (Albert, Martin, and Lewis, 1980) also may be effective."*
Trials included	(Albert, Martin, and Lewis, 1980; Bullard, Liaw, Tsai, et al., 1996; Davies, Angus, and Calverley, 1999; Emerman, Connors, Lukens, et al., 1989b; Niewoehner, Erbland, Deupree, et al., 1999; Thompson, Nielson, Carvalho, et al., 1996).
ID	1145

Author / Title / Reference / Yr	Davies, L., Angus, R. M., & Calverley, P. M. A. 1999, "Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial", *Lancet*, vol. 354, no. 9177, pp. 456-460. Ref ID: 217
N=	N= 56, UK, 1 site only, follow up to 6 weeks
Research Design	RCT
Aim	A trial to test the hypothesis that oral prednisolone would not modify the rate of improvement of lung function or reduce hospital stay in patients admitted with acute exacerbations of COPD
Operational Definition	No details given for definition of COPD used for study
Population	Patients with diagnosed COPD with 48hrs+ of increased cough frequency or severity, increased sputum volume or purulence, and increased wheeze
Intervention	N=29 An intervention with 30mg prednisolone once daily for 14 days
Comparison	N=27 Control group of matching placebo
Outcome	The main outcomes studied were changes in FEV1 (% of predicted) from baseline to discharge then at 6 weeks. Also the length of hospital stay for the index admission was recorded, and changes in QOL measures and side effects all assessed at 6 weeks
Characteristics	Age =67yrs, Male =68%, Smoking =55 pack-years, FEV1 % predicted before bronchodilation =24.7%
Results	**Spirometry** Up to day 5 the post bronchodilation FEV1 increased in the corticosteroid group by 90ml per day compared to an increase of 30ml per day in placebo patients (p=0.039) At 6 weeks the percentage predicted FEV1 after bronchodilation was 39.6% for the corticosteroid group compared to only 33.2% in the placebo group, which were not significantly different to discharge values **Length of Stay** In terms of duration of hospital admission an intention to treat analysis found that the median length of stay amongst patients in the steroid arm was 7 days which was significantly shorter then the 9 days for patients in the placebo arm (p=0.027) **QOL** Visual analogue scales were used to measure how patients felt on discharge compared to admission and found improvements in both study arms Decreases in symptom scores were seen in both treatment groups **Adverse events** Three patients in the corticosteroid group and 2 patients in the placebo group reported heartburn. 6 patients in the steroid treated arm developed transient glycosuria
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	217

Author / Title / Reference / Yr	Niewoehner, D. E., Erbland, M. L., Deupree, R. H., Collins, D., Gross, N. J., Light, R. W., Anderson, P., & Morgan, M. A. 1999, "Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease", *New England Journal of Medicine*, vol. 340, no. 25, pp. 1941-1947. Ref ID: 36
N=	N=271, USA, 27 sites, follow up to six months
Research Design	RCT
Aim	A trial to evaluate the efficacy of systemic glucocorticoids for exacerbations of COPD, and to determine the optimum length of treatment
Operational Definition	No definition of COPD or exacerbation stated
Population	A clinical diagnosis of an exacerbation of COPD
Intervention	N=80 The intervention tested was intravenous methylprednisolone at 125mg every 6 hours for 72 hours followed by (2 week group) oral prednisolone at 60mg to 20 mg for 2 weeks then placebo to 8 weeks, or n=80 (8 week group) oral prednisolone 60mg to 5 mg for 8 weeks
Comparison	N=111 A control of IV dextrose solution then matching placebo capsules to 8 weeks (placebo group)
Outcome	The primary endpoint was treatment failure, a composite of all cause mortality, need for intubation, readmission with COPD, or intensification of therapy. Secondary endpoints were change in FEV1 with spirometry to standard practice, length of stay, and death from any cause. All measured at various time points to 6 months. In addition patients were evaluated for all adverse events at each study visit
Characteristics	The population is taken from patients at Veterans affairs centres. Age =68yrs, Male =99%, COPD hospitalisation in previous 2 years =68%, Cigarette smoking =75 pack years (with significant difference between groups), FEV1 =0.77l
Results	**Treatment Failure** The primary end point of treatment failure found a significant difference in failure rates between the intervention arms (23%) and placebo arms (33%) at 30 days (p =0.04), and also at 90 days (37% Vs 48%) (p=0.04), but this difference was not maintained to 6 months. The duration of therapy for either 2 or 8 weeks did not appear to have any significant effect on this outcome **Length of stay** The length of initial hospitalisation was shorter in patients treated with steroids at 8.5 days compared to 9.7 days for patients on placebo (p=0.03). There were no significant differences between time hospitalised between the study groups for subsequent events to 6 months for either COPD or non COPD admissions Lung function Although patients given steroids were found to recover FEV1 more quickly than those on placebo 0.96l Vs 0.87l to 3 days, no such difference was not noted at 2 weeks or subsequently to 6 months **All cause mortality** There were no significant differences on mortality rates between the treatment arms to 6 months **Adverse events** A greater proportion of the patients treated with glucocorticoids (15%) than with placebo (4%) required treatment for hyperglycaemia (p=0.002). Adverse events defined as 'other' were more common among patients receiving steroids than placebo (p=0.04) **Sub-group analysis** In pre-defined sub group analysis treatment with glucocorticoids appears to have a more favourable outcome in terms of patients who had previously been hospitalised with COPD than those who had not OR 4.6 (95% CI

	1.4 to 14.8), where patients had a COPD admission history the treatment failure rate on steroids was 49.5% compared to 66.7% on placebo
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	36

Author / Title / Reference / Yr	Bullard, M. J., Liaw, S. J., Tsai, Y. H., & Min, H. P. 1996, "Early corticosteroid use in acute exacerbations of chronic airflow obstruction.", *American Journal of Emergency Medicine.*, vol. 14, no. 2, pp. 139-143. Ref ID: 1360
N=	N=113, Taiwan, 1 site only, follow up to 6 weeks
Research Design	RCT
Aim	A study to determine whether en early intervention of corticosteroids for patients with acute exacerbations of COPD provides measurable benefit over placebo
Operational Definition	No definition for COPD is stated
Population	Patients with suspected chronic airflow obstruction with presenting dyspnoea and FEV1 <60% predicted, with FEV1/ FVC of <60%
Intervention	N=60 An intervention with 100mg of hydrocortisone IV every 4 hours for 4 days, then 40mg (oral) prednisolone daily for 4 days
Comparison	N=53 Patients in the control arm received matching placebo
Outcome	Pulmonary function tests were undertaken at regular intervals to 6 hours, in addition to absolute changes, the number of patients improving their PERF or FEV1 by more than 40% was also analysed. Also a six-point scale for changes in patients subjective assessment employed over the same time. 6-week outcomes included length of stay, in-hospital mortality, and the requirement for intubation.
Characteristics	Age =66yrs, Male =86%, FEV1 =0.53l, pH =7.4, all presenting with dyspnoea
Results	**Lung function** At 6 hours patients in the steroid treated group showed significant improvement over baseline for PEFR 21.71l/min and FEV1 0.14l compared to only minimal improvements were found among patients on placebo 5.52l/min and 0.02l respectively. There was no significant difference between the number of patients demonstrating a 40% improvement in these parameters between the two groups to 6 weeks **Patient self-assessment** both of the study groups reported improvements in subjective self-reporting scale of symptom limitation. **Length of stay** The average length of stay for the index admission for those initially treated with steroids was 9 days whereas for the placebo group the initial admission length was 14 days

SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b
NCC CC ID	1360

COPD Evidence Tables

The evidence tables are presented in section order.

The methodological quality of each paper was rated using the Scottish Intercollegiate Guidelines Network (SIGN) system (Scottish Intercollegiate Guidelines Network. SIGN 50 Guideline Developers Handbook, 2001; ID 19457):

++	All or most of the SIGN methodology checklist criteria were fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
+	Some of the criteria were fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
-	Few or no criteria were fulfilled. The conclusions of the study are thought likely or very likely to alter.

Chronic Obstructive Pulmonary Disease: Management of adults with Chronic Obstructive Pulmonary Disease in Primary and Secondary Care

Management of exacerbations of COPD
Antibiotics
Index

Author	Publication Date	ID
Scottish Intercollegiate Guidelines Network (SIGN). Community management of lower respiratory tract infection (LRTI) in adults. Guideline 59. Section 4 Exacerbations of COPD. Point 4.2 Treatments. June 2002	2002	1316
McCrory, D. C., Brown, C., Gray, R. N., Goslin, R. E., MacIntyre, N. R., Kolimaga, J. T., Oddone, E. Z., & Matchar, D. 2001, *Management of acute exacerbations of chronic obstructive pulmonary disease.*, Agency for Healthcare Research and Quality., Rockville, MD, USA, 256.	2001	1145
Nouira, S., Marghli, S., Belghith, M., Besbes, L., Elatrous, S., & Abroug, F. 2001, "Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: A randomised placebo-controlled trial", *Lancet*, vol. 15, no. 9298, p. pp-2025.	2001	349
Allegra, L., Blasi, F., de Bernardi, B., Cosentini, R., & Tarsia, P. 2001, "Antibiotic treatment and baseline severity of disease in acute exacerbations of chronic bronchitis: a re-evaluation of previously published data of a placebo-controlled randomized study", *Pulmonary Pharmacology & Therapeutics*, vol. 14, pp. 149-155.	2001	1151
Sin, D. D. & Tu, J. V. 2000, "Outpatient antibiotic therapy and short term mortality in	2000	416

elderly patients with chronic obstructive pulmonary disease", *Canadian Respiratory Journal*, vol. 7, no. 6, pp. 466-471.		
Saint, S., Bent, S., Vittinghoff, E., & Grady, D. 1995, "Antibiotics in chronic obstructive pulmonary disease exacerbations – a meta analysis", *Jama-Journal of the American Medical Association*, vol. 273, no. 12, pp. 957-960.	1995	44
Ball, P., Harris, J. M., Lowson, D., Tillotson, G., & Wilson, R. 1995, "Acute infective exacerbations of chronic bronchitis", *Quarterly Journal of Medicine*, vol. 88, no. 1, pp. 61-68.	1995	1152

Author / Title / Reference / Yr	Scottish Intercollegiate Guidelines Network (SIGN). Community management of lower respiratory tract infection (LRTI) in adults. Guideline 59. Section 4 Exacerbations of COPD. Point 4.2 Treatments. June 2002
Research Design	SIGN Guideline
Aim	The guideline focuses on the following in LRTI management: 1. When should antibiotics be prescribed? 2. How can the rates of re consultation be reduced? 3. When should patients be referred to secondary care? This evidence table focused on point 1 in application to exacerbations of COPD
Operational Definition	Guideline states, "There is currently no general agreement on the definition of an exacerbation in COPD. Definitions of exacerbations in COPD are based on increasing symptoms and / or increased health care utilisation (RCP 2002). In some studies exacerbations have been defined in operative terms according to the type and number of symptoms. A commonly used definition is based on an increase in symptoms of dyspnoea, sputum volume and sputum purulence with or without symptoms of upper respiratory infection. (Anthonisen, Manfreda Warren et al 1987).
Population	Exacerbations of COPD
Treatment	This section is quoted directly from the guidelines: "There have been a number of randomised placebo controlled trials of antibiotic therapy (usually aminopenicillin or tetracycline) in pts with exacerbation of COPD. A systematic review of these trials has shown a small benefit for those patients receiving antibiotic rather than placebo. Although a small number of pts was used in each of the original study groups (Saint et al 1995). **Evidence level 1-**

	In one study the sub-group of patients showing most benefit from antibiotics were those with two or all of the following symptoms: increasing breathlessness, sputum volume and sputum purulence (Anthonisen et al 1987). Patients in this study had significant baseline obstruction with a mean FEV1 of 33% of predicted. In pts with COPD, sputum purulence is a good guide to the presence and number of bacteria and whether antibiotic treatment is likely to be beneficial (Sethi et al 2001) (Niroumand 1998). **Evidence level 1.** **Recommendation** Patients with significant airway obstruction who have an increase in breathlessness and sputum purulence should be treated with an antibiotic**.** Grade B **Good practice point** The antibiotic of choice should be an aminopenicillin, a macrolide or a tetracycline. Quinolones have performed equally well in clinical trials, but no clinical superiority over other antibiotics has yet been shown. (Davies 1986)".
SIGN Quality Rating	Key to evidence statements and grades of recommendations used by this SIGN guideline (assigned by SIGN team and not NCC CC Systematic Reviewer): **Levels of evidence** 1++ High quality meta analyses, systematic reviews of RCTs or RCTs with a very low risk of bias. 1+ Well conducted meta analyses, systematic reviews, or RCTs with a low risk of bias. 1- Meta analyses, systematic reviews or RCTs with a high risk of bias. 2++ High quality systematic review of case control or cohort or studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal. 2+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal. 2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal. 3 Non analytic studies, e.g. case reports, case series 4 Expert opinion. **Grades of recommendations** Grade B - A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results: or extrapolated evidence from studies rated as 1++ or 1+.
Hierarchy of Evidence Grading	SIGN Guideline
References	Anthonisen NR, Manfreda J, Warren CP et al. Antibiotic therapy in exacerbations of COPD. Ann Intern Med. 1987. 106: 196-204. Davies BI, Maesen FP. Quinolones in chest infections. J Antimicrob Chemother 1986; 18: 296-9. Niroumand M, Grossman RF. Airway infection. Infect Dis Clin North Am 1998 12: 671-88 RCP Consensus statement on COPD. Edinburgh: The College; 2002

	Saint S, Bent S, Vittinghoff E et al. Antibiotics in COPD exacerbations. A meta-analysis. JAMA 1995; 273: 957-60 Sethi S, Murphy TF. Bacterial infection in COPD in 2000: a state-of-the-art review. Clin Microbiol Rev 2001; 14: 336-63
NCC CC ID	1316

Author / Title / Reference / Yr	McCrory, D. C., Brown, C., Gray, R. N., Goslin, R. E., MacIntyre, N. R., Kolimaga, J. T., Oddone, E. Z., & Matchar, D. 2001, *Management of acute exacerbations of chronic obstructive pulmonary disease.*, Agency for Healthcare Research and Quality., Rockville, MD, USA, 256. Ref ID: 1145
N=	N=1 meta-analysis (Saint, Bent, Vittinghoff et al 1995 – See Evidence Table ID 44). Nine trials included in the meta analysis. Authors required studies to consider at least a 5-day duration of follow up. All antibiotic agents were considered together in the analysis. Adjustments were made for trials that used the number of exacerbations instead of the number of pts as the unit of analysis. N=11 placebo-controlled studies of antibiotic treatment. (Listed below). Two of the trials were included by AHRQ but were excluded from the meta analysis because one trial did not report outcomes as continuous variables (Pines, Raafat, Plucinski et al 1968) and the other was published after the meta-analysis was performed (Sachs, Koeter, Groenier et al 1995). Two other trials were excluded because one was reported in a letter (Manresa, Blavia, Martin et al 1987) and the other one was published in Italian (Allegra, Grassi, Grossi et al 1991).
Design	"In the preliminary literature review, AHRQ identified several hundred head-to-head comparisons of different antibiotic treatments for acute exacerbation of COPD. The Advisory Panel of Technical Experts suggested limiting the studies of antibiotic treatment to placebo-controlled trials. There was concern that this large and complex review could command all the resources that were available to the AHRQ project, to the exclusion of other questions".
Aim	How effective are the medical modalities (**antibiotics)** that are used to treat acute exacerbations of COPD in alleviating symptoms, resolving the cause of the exacerbation, preventing hospital admissions and decreasing LOS?
Operational Definition	Adults who had COPD based on clinical diagnosis, spirometry or known or suspected history; subjects must have been experiencing an acute exacerbation of respiratory symptoms. Respiratory symptoms included dyspnoea, increased quantity or purulence of sputum or acute respiratory failure.
Population	Acute exacerbations of COPD
Intervention	Antibiotic drugs studied were tetracycline, doxycycline, chloramphenicol, penicillin, streptomycin, ampicillin, amoxicillin and cotrimoxazole.
Comparison	Placebo
Outcome	PEFR, duration of exacerbation, PaO2, symptom score, and overall score by physician.
SIGN Quality Rating	++

Hierarchy of Evidence Grading	1a
Results	The results presented here have been quoted directly from the AHQR report section entitled "Selected Treatment Strategies – Antibiotics" pp. 48-51. **"Meta analysis of the 9 trials:** • Three (individually) found statistically significant effects favouring antibiotics compared to placebo (Anthonisen, Manfreda, Warren et al 1987, Berry, Fry, Hindley et al 1960, Pines, Raafat, Greenfield et al 1972). • Three trials suggested a trend favouring antibiotics (Elmes, Fletcher and Dutton 1957, Elmes, King, Langlands et al 1965, and Fear, Edwards 1962. • Three trials failed to show any difference from placebo (Jorgensen, Coolidge, Pedersen et al 1992, Nicotra, Rivera and Awe 1982, Petersen, Esmann, Honcke et al 1967). • Results were combined to give an overall estimate of 0.22 (95% CI 0.1 to 0.34), a small but statistically significant effect favouring antibiotics over placebo. **Subgroup analysis:** PEFR (most frequently reported outcome measure (reported in 6 of the 9 trials)) One trial showed a statistically significant improvement in PEFR favouring antibiotics (Anthonisen, Manfreda, Warren et al 1987) and one trial showed a trend (Elmes, King, Langlands et al 1965). The trials were statistically homogeneous. A combined estimate of the difference in mean PEFR between antibiotic and placebo treated participants was 10.75 L/minute (95% CI, 4.96 to 16.54). **Level of care** Outpatient versus inpatient care. The summary effect size for outpatient studies was 0.17 (95%CI, 0.03 to 0.30) and 0.38 (95%CI, 0.13 to 0.62) for hospitalised patients. **Bacterial infection and severity of illness** In the meta analysis, it was not possible to investigate a relationship between antibiotic efficacy and severity of illness, sputum purulence, or bacterial cultures. Several of the trials analysed the efficacy of antibiotics according to subgroups that were defined either by evidence of bacterial infection or severity of illness (Anthonisen, Manfreda, Warren et al 1987, Berry, Fry, Hindley et al 1960 Elmes, King, Langlands et al 1965). Anthonisen, Mangreda, Warren et al 1987 found that a priori criteria that were proposed to select patients with signs of infection (Winnipeg criteria) showed a relationship of better outcomes with antibiotic versus placebo treatment. Pts with type-1 exacerbations (who met all three criteria: increases in amount of sputum, purulence of sputum and dyspnoea) benefited the most, with resolution of symptoms in 63% of the antibiotic treated exacerbations and 43% of the placebo treated exacerbations. Pts with type-3 exacerbations (who met one of the above three criteria) did not show any benefit, with 74% of exacerbations resolving on antibiotics and 70% resolving on placebo. Those with type-2 exacerbations (who met two of the above three criteria) showed an intermediate (and not statistically significant) benefit, with 70%

	resolving on antibiotics and 60% resolving on placebo. Berry, Fry, Hindley et al 1960 assessed the severity of exacerbation at presentation on a subjective 4-point scale (baseline, mild, moderate or severe). For pts presenting with mild exacerbations there were no significant difference in severity of symptoms between antibiotic and placebo patients at any time point (two days, one wk and two wks). For pts presenting with moderate or severe exacerbations, antibiotic pts had significantly less severe symptoms on days 2 and 7 but were not significant at two wks. (Differences not quoted). Elmes, King, Langlands et al 1965 matched pts based on severity of illness which was defined as two or more criteria (temp higher than 37.5degrees cent, pulmonary consolidation or purulent sputum). The trial was not blinded to bacteriologic results. A later independent, blinded assessment failed to find a significant difference between antibiotic and placebo participants. Different trial populations appear to have clinically important differences in severity of illness (see attached table). **Adverse Effects** The most common adverse effect was diarrhoea, which was observed in the placebo group to four trials that described adverse effects in detail (Anthonisen, Manfreda, Warren, et al 1987, Elmes, Fletcher and Dutton 1957, Elmes, King, Langlands et al 1965, Jorgensen, Coolidge, Pedersen et al 1992)." **The AHQR authors conclude that in acute exacerbations of COPD:** **"**RCTs of antibiotic versus placebo treatment demonstrated improvement in pulmonary function. Trials suggest that the greater degree of bacterial infection (sputum purulence) and severe illness (worse PEFR) the greater degree of benefit from antibiotics, however this has not been conclusively demonstrated".
Studies Included	Meta-analysis by Saint, Bent, Vittinghoff et al 1995, included nine trials: Anthonisen, Manfreda, Warren et al 1987 (N=310), Berry, Fry, Hindley et al 1960 (N=33), Elmes, Fletcher, Dutton 1957 (N=113), Elmes, King, Langlands et al 1965 (N=56), Fear and Edwards 1962 (N=119), Jorgensen, Coolidge, Pedersen et al 1992 (N=262), Nicotra, Rivera and Awe 1982 (N=40), Petersen, Esmann, Honcke et al 1967 (N=19), Pines, Raafat, Greenfield et al 1972 (N=149). RCTs: Anthonisen, Manfreda, Warren et al 1987, Berry, Fry, Hindley, et al 1960, Elmes, Fletcher, Dutton 1957, Elmes, King, Langlands et al 1965, Fear and Edwards 1962, Jorgensen, Coolidge, Pedersen et al 1992, Nicotra, Rivera and Awe 1982, Petersen, Esmann, Honcke et al 1967, Pines, Raafat, Plucinski et al 1968, Sachs, Koeter, Groenier et al 1995.
ID	1145

Author / Title / Reference / Yr	Nouira, S., Marghli, S., Belghith, M., Besbes, L., Elatrous, S., & Abroug, F. 2001, "Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: A randomised placebo-controlled trial"

	Lancet, vol. 15, no. 9298, p. pp-2025. Ref ID: 349
N=	N= 93 patients. Sites=Two hospitals. Duration=Jan 1996 to Dec 1999. Geographical location=Tunisia (N=3 excluded secondarily for non-invasive ventilation<6hrs).
Research Design	Prospective, randomised, double-blind, placebo-controlled RCT
Aim	To assess the efficacy of oral ofloxacin in the treatment of patients admitted to the ICU
Operational Definition	Exacerbation diagnosed on the basis of clinical history, physical examination and CXR. Acute respiratory failure requiring mechanical ventilation within the first 24 hr of admission – ARF defined as association of exacerbation of dyspnoea with at least two of the following: respiratory rate greater than 30 bpm; arterial partial pressure of CO2 greater than 6kPa; and arterial pH <7.30 after the pt had been breathing spontaneously for at least 10 min.
Population	Severe acute exacerbation of COPD requiring mechanical ventilation. "Patients were systematically assigned non-invasive ventilation. In case of failure of non-invasive ventilation or contraindication, patients were intubated and mechanically ventilated in the assist-control mode".
Intervention	Once daily does of ofloxacin 400mg. All treatments were given orally as two tables of 200 mg every day for 10 consecutive days in the morning. Intubated patients were given the same regimen via a NGT. Patients transferred from the ICU to another ward during this 10-day period were asked to complete the study treatment with the agreement of their physician. N=45
Comparison	Matched placebo N=45
Outcomes	Primary study outcomes: Death in hospital / need for additional course of antibiotics. Secondary study outcomes: Duration of mechanical ventilation / length of hospital stay.
Characteristics	Mean age 66 yrs Gender 90% male Baseline FEV1 antibiotic group 0.79 (0.25), placebo group 0.74 (0.23) (L/s) Initial ventilatory support – non-invasive 69% approx each group. Concomitant drugs 64% antibiotic group, 69% placebo group.
Results	**Deaths** 4% (N=2) patients receiving ofloxacin and 22% (N=10) in the placebo group died in hospital. Absolute risk reduction (ARR) 17.5%, 95% CI, 4.3 to 30.7, p=0.01. There were five times more deaths in hospital in the placebo group than in the ofloxacin group **Additional courses of antibiotics** 6% (N=3) patients receiving ofloxacin and 35% (N=16) in the placebo group required additional antibiotics.

	Treatment with ofloxacin significantly reduced the need for additional courses of antibiotics. ARR 28.4%, 95% CI, 12.9 to 43.9, p=0.0006. **Combined frequency of death in hospital and need for additional antibiotics** Was significantly lower in patients in the ofloxacin group than in those receiving placebo. ARR 45.9%, 95% CI, 29.1 to 62.7, p<0.0001. **Duration of mechanical ventilation** Was significantly shorter in the ofloxacin group than in the placebo group. Absolute difference 4.2 days, 95% CI, 2.5 to 5.9. **Duration of hospital stay** Was significantly shorter in the ofloxacin group than in the placebo group. Absolute difference 9.6 days, 95% CI, 3.4 to 12.8. **Nonsocomial pneumonia** Pts in the ofloxacin group were less likely to develop pneumonia than those in the placebo group, especially during the first week of mechanical ventilation. In the placebo group, most episodes of nosocomial pneumonia occurred within the first wk after admission to ICU (mean 7.2 days, SD 2.2, range 4 to 11) whereas all episodes in the ofloxacin group arose after this time (10.6 days, 2.9, 9 to 14; p=0.04). The mortality rate in the ICU was significantly higher in pts with nosocomial pneumonia than in those without this complication 13% (N=4/13) vs 8% (N=6/77), p=0.01). **Conclusion:** New fluoroquinolones, such as ofloxacin are beneficial in the treatment of COPD exacerbation requiring mechanical ventilation.
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1b
NCC CC ID	349

Author / Title / Reference / Yr	Allegra, L., Blasi, F., de Bernardi, B., Cosentini, R., & Tarsia, P. 2001, "Antibiotic treatment and baseline severity of disease in acute exacerbations of chronic bronchitis: a re-evaluation of previously published data of a placebo-controlled randomized study", *Pulmonary Pharmacology & Therapeutics*, vol. 14, pp. 149-155. Ref ID: 1151
N=	N=46 Italian General Hospitals or University Hospitals. Date period – Eligible pts were followed as outpatients for the original study from Oct 1989 through to April 1990. Original RCT: N=957 screened / N=761 eligible / N=761 followed up / N=369 pts with first exacerbation randomised

	N=190 antibiotics / N=179 placebo 176 antibiotic group analysed (14 drop-out) 159 placebo group analysed (20 drop-out) Total N=335 The authors then retrospectively analysed the reported study data by re clustering pts on the basis of severity of baseline lung function. Cluster 1 N=104 / Cluster 2 N=109 / Cluster 3 N=122 / Total N=335
Research Design	Retrospective data analysis of a previously reported RCT
Aim	Antibiotic associated improvement may be particularly significant in pts with greater baseline pulmonary dysfunction although it is unclear whether all COPD pts need antibiotic treatment. In order to provide additional proof of the utility of antibiotic treatment in acute exacerbations of chronic bronchitis authors extended retrospectively the analysis on a previously reported study carried out within a relevant population.
Operational Definition	Scale fully documented to define exacerbation (unclear whether validated scale and scoring system).
Population	Acute exacerbations chronic bronchitis (asthmatics excluded)
Intervention	Amoxicillin-clavulanic acid 1g b.d. for 5 days
Comparison	Matched placebo for 5 days
Outcomes	FEV1
Retrospective re-clustering	Pts were retrospectively re-clustered on the basis of severity of baseline lung function: Cluster 1 mean screening FEV1 32.67+/- 6.83(SD) Cluster 2 mean screening FEV1 54.12 +/- 5.56 Cluster 3 mean screening FEV1 71.54 +/- 5.51
Characteristics	Gender m/f 246 / 89 Age 62.8yrs mean (Pts considered eligible if aged over 40 yrs) Pts receiving antibiotic or steroid therapy were excluded. FEV1 screening in antibiotic group 1.53 +/- 0.57 FEV1 screening in placebo group 1.49 +/- 0.51 FEV1 admission in antibiotic group 1.38 +/- 0.52 FEV1 admission in placebo group 1.35 +/- 0.51
Results	When clinical improvement was analysed on the basis of patient re clustering: **Mean number of exacerbations during the 12 months prior to enrolment** Cluster 1 = 3.05 +/- 0.96 Clusters 2 and 3 = 1.61 +/- 1.03 ($p<0.001$) **Cluster 1 (severe COPD)**

	31.4% pts treated with antibiotics showed clinical improvement and 58.8% successfully recovered 13.2% pts receiving placebo improved and 17% successfully recovered (p<0.001) **Cluster 2 and 3 (grouped together)** 31.2% improvements and 53.6% recovered pts among antibiotic treated group 29.2% improvements and 30.2% successful recoveries among placebo pts (p<0.001) **Placebo treated group** The improvement / success vs failure rate was significantly different in Cluster 1 patients compared to Cluster 2 and 3 patients (p<0.01). **Differences in final FEV1 values** In the treatment group and placebo group were significantly different (p<0.01) in favour or the active treatment group. **Comparison between screening and follow-up** Among cluster 1 subjects, the comparison between screening and follow up FEV1 values showed an improvement following antibiotic treatment and worsening after placebo (p<0.01). In cluster 2 and 3 the difference between screening and follow up FEV1 values was not significant for both treatment groups. In patients with severe functional impairment and higher number of exacerbations per year are those who derive the greatest benefit from antibiotic treatment.
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1b – Caution this grading is attributed to the original study. The data presented in the evidence table is post hoc / retrospective analysis of previously reported RCT data. Retrospective re-clustered patients on the basis of severity of baseline lung function.
NCC CC ID	1151

Author / Title / Reference / Yr	Sin, D. D. & Tu, J. V. 2000, "Outpatient antibiotic therapy and short term mortality in elderly patients with chronic obstructive pulmonary disease", *Canadian Respiratory Journal*, vol. 7, no. 6, pp. 466-471. Ref ID: 416
N=	N=26,301. Geographical location=Canada
Research Design	A population-based retrospective cohort study
Aim	To determine the association between outpatient use of oral antibiotics and 30-day all-cause mortality following hospitalisation in a group of elderly COPD patients.
Operational Definition	COPD defined using ICD-9 codes (International Classification of Diseases, ninth revision).
Population	Patients aged 65 yrs or older who were hospitalised for COPD between 1992 and 1996.
Factor of interest	• Elderly pts admitted at least once with an ICD-9 diagnosis of COPD were identified through the Canadian

	Institute for Health Information database. • The data was then linked to the Ontario Drug Benefit database to determine the use of antibiotics within 30-days of the index hospitalisation. • Relevant data was then matched to the Ontario registered persons database to determine the 30-day mortality following the index hospitalisation.
Medical information	• For those with multiple admissions, only the initial hospitalisation was used in the analysis in order to avoid double counting of pts. • Pts transferred from chronic care to acute care were excluded because outpatient drug information was unavailable. • Pts younger than 65yrs were excluded as the databases did not contain any prescription medication information for this group. • During the study period the Ontario government offered prescription medication free of charge. • The Ontario Drug Benefit database contained comprehensive data on all outpatient medications including the name, the formulation and the amount that was dispensed to all pts in the cohort. • From the database, the use of oral antibiotics within 30-days of the index hospitalisation was ascertained. • Medications selected were amoxicillin (ampicillin), penicillin, sulfa drugs, cephalosporins, fluoroquinolones, tetracyclines and macrolides. • By law, all deaths occurring in Ontario must be reported. The information is then registered on the Ontario Registered Persons Database. This database was used in the present study to determine mortality.
Outcomes	14-day and 30-day mortality from the date of the index hospitalisation. Use of antibiotics within 30-days before the index hospitalisation.
Characteristics	Mean age 75yrs
Results	**Demographics** • N=26,301 pts included in the study • 7% (N=1937) of pts died within 30-days of hospitalisation • 34% (N=9037) of the pts used an oral antibiotic within 30 days of their index hospitalisation date. • Pts who were 80 yrs of age or older had the highest rate of antibiotic use (30%), while those between 65-70yrs had the lowest rate of use (22%). • The Charlson-Deyo co morbidity scores were similar between the two groups*. **Mortality** • Patients who used antibiotics within 30-days of the index hospitalisation date experience lower odds for all-cause 30-day mortality after hospitalisation than those who did not receive antibiotics. • Odds ratio (OR) 0.83, 95% CI, 0.75 to 0.92. (N.B This result takes into account adjustments made for important baseline covariates including age, sex, Charlson-Deyo co morbidity scores and use of other COPD medications).

	• 14-day mortality – relative odds associated with antibiotic exposure before hospitalisation was 0.79, 95% CI, 0.70 to 0.90 **Antibiotics** • Use of macrolides had the lowest relative odds for mortality. • OR 0.58, 95% CI, 0.47 to 0.73 • Use of fluoroquinolones had the highest relative odds. • OR 0.98, 95% CI, 0.84 to 1.15 **Conclusion:** In elderly pts with COPD who required hospitalisation for COPD, treatment with oral antibiotics on an outpatient basis before the COPD related admission was associated with a reduced mortality rate. COPD pts who received at least one course of antibiotic therapy before hospitalisation were 17% less likely to die within 30-days following hospitalisation for their COPD than those who did not receive any antibiotic therapy.
SIGN Quality Rating	++
Hierarchy of Evidence Grading	III
NCC CC ID	416

Author / Title / Reference / Yr	Saint, S., Bent, S., Vittinghoff, E., & Grady, D. 1995, "Antibiotics in chronic obstructive pulmonary disease exacerbations. A Meta analysis", *Jama-Journal of the American Medical Association*, vol. 273, no. 12, pp. 957-960. Ref ID: 44
N=	N=9 trials (1,101 pts) of which 6 included PEFR as an outcome measure (836 pts)
Research Design	Meta analysis of RCTs
Aim	To estimate the effectiveness of antibiotics in treating exacerbations of COPD
Operational Definition	Participants with a diagnosis of COPD (chronic bronchitis or emphysema) and thought to be having an exacerbation followed up for at least 5 days.
Population	In and out patients with acute exacerbation of COPD
Intervention	Antibiotic regimens including oxytetracycline, ampicillin, chloramphenical, amoxicillin, tetracycline and a combination of sulfamethoxazole and trimethoprim, amoxicillin or doxycycline.
Comparison	Placebo
Outcomes	Days of illness, overall symptom score, overall score by physician and change in peak expiratory flow rate.

Characteristics	Not documented
Results	**See AHRQ Evidence Table ID 1145** In summary: Overall summary effect size of the 9 trials was 0.22 (95% CI, 0.10 to 0.34) indicating a small benefit in the antibiotic treated group. Similar analysis of the 6 studies that provided data on PEFR changes revealed a summary effect size of 0.19 (95% CI, 0.03 to 0.35) and a summary change in PEFR of 10.75 L/min (95% CI, 4.96 to 16.54) in four of the antibiotic treated group. Sensitivity analyses did not significantly affect the results.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1a
NCC CC ID	44

Author / Title / Reference / Yr	Ball, P., Harris, J. M., Lowson, D., Tillotson, G., & Wilson, R. 1995, "Acute infective exacerbations of chronic bronchitis", *Quarterly Journal of Medicine*, vol. 88, no. 1, pp. 61-68. Ref ID: 1152
N=	N=127 GPs joined the study / N=471 pts entered / N=48 (10%) lost to F/U / N=423 outcome fully documented Geographical location = UK. Duration=Nov 1992 to March 1993.
Research Design	Computer based general practice prospective data collection study
Aim	To determine whether feature of past history, presenting symptoms, or findings on examination were **predictive** of failure to recover from a COPD exacerbation.
Operational Definition	No operational definitions provided.
Population	Patients presenting with acute infective exacerbations of chronic bronchitis
Data collection	• GP computer network which recorded history, examination findings and management decisions. • If pt returned for any reason to the practice during the next 28 days from the first presentation the reason for return and details were recorded. • Data was analysed in stages: 1) First analysis was of factors relating to the pts past and current history at the time of presentation. 2) Second analysis was undertaken at the 4 wk follow up visit when outcome was assessed, attempted to relate the variables to outcome so as to establish which features were predictive of particular clinical results. 3) In addition, an aggregate clinical score thought to be representative of severity of an exacerbation was calculated.
Characteristics	Median age 68 yrs. Range 31 to 94 yrs. / Gender – 56% male / 82% current or ex smokers
Results	• The only factors significantly ($p<0.05$) predicting failure to recover from an acute exacerbation of chronic bronchitis were historical.

	• The best combination predicting return with a chest problem was history of cardiopulmonary disease (OR 2.30, 95% CI, 1.30 to 4.10) and more than four previous exacerbation in the last 12 months (OR 2.11, 95% CI, 1.05 to 4.23). The sensitivity was 75% and specificity 47%.
SIGN Quality Rating	-
Hierarchy of Evidence Grading	III
NCC CC ID	1152

Chronic Obstructive Pulmonary Disease: Management of adults with Chronic Obstructive Pulmonary Disease in Primary and Secondary Care

Management of exacerbations of COPD
Theophylline and other methylxanthines
Index

Author	Publication Date	ID
Barr RG, Rowe BH, Camargo CA Jr. Methylxanthines for exacerbations of chronic obstructive pulmonary disease (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2003. Oxford: Update Software. CD002168	2002	859

Reference Exclusion List
Original literature search N=121 hits

Reference	Reason for exclusion
Rice, K. L., Leatherman, J. W., Duane, P. G., Snyder, L. S., Harmon, K. R., Abel, J., & Niewoehner, D. E. 1987, "Aminophylline for acute exacerbations of chronic obstructive pulmonary disease. A controlled trial", *Annals of Internal Medicine*, vol. 107, pp. 305-309. Ref ID: 1110	Included in Cochrane
Seidenfeld, J. J., Jones, W. N., Moss, R. E., & Tremper, J. 1984, "Intravenous aminophylline in the treatment of acute bronchospastic exacerbations of chronic obstructive pulmonary disease", *ANN EMERG.MED*, vol. 13, pp. 248-252. Ref ID: 1111	Included in Cochrane
Dolcetti, A., Osella, D., De Filippis, G., Carnuccio, C., & Grossi, E. 1988, "Comparison of intravenously administered doxofylline and placebo for the treatment of severe acute airways obstruction", *Journal of International Medical Research*, vol. 16, pp. 264-269. Ref ID: 1107	Included in Cochrane
Wrenn, K., Slovis, C. M., Murphy, F., & Greenberg, R. S. 1991, "Aminophylline therapy for acute bronchospastic disease in the emergency room", *Annals of Internal Medicine*, vol. 115, no. 4, pp. 241-247. Ref ID: 1289	Included in Cochrane
Tandon, M. K. & Kailis, S. G. 1991, "Bronchodilator treatment for partially reversible chronic obstructive airways disease", *Thorax*, vol. 46, no. 4, pp. 248-251. Ref ID: 496	Stable COPD

Barbera, J. A., Reyes, A., Roca, J., Montserrat, J. M., Wagner, P. D., & Rodriguez, R. R. 1992, "Effect of intravenously administered aminophylline on ventilation/perfusion inequality during recovery from exacerbations of chronic obstructive pulmonary disease", *American Review of Respiratory Disease*, vol. 145, pp. 1328-1333. Ref ID: 1106	N=9 / Recovery from exacerbation of COPD
Murata, G. H., Gorby, M. S., Chick, T. W., & Halperin, A. K. 1990, "Aminophylline in the outpatient management of decompensated chronic obstructive pulmonary disease", *Chest*, vol. 98, no. 6, pp. 1346-1350. Ref ID: 93	Outpatient management
ZuWallack, R. L., Mahler, D. A., Reilly, D., Church, N., Emmett, A., Rickard, K., & Knobil, K. 2001, "Salmeterol plus theophylline combination therapy in the treatment of COPD", *Chest*, vol. 119, no. 6, pp. 1661-1670. Ref ID: 1118	Stable COPD
Rossi, A., Kristufek, P., Levine, B. E., Thomson, M. H., Till, D., Kottakis, J., & Della Cioppa, G. 2002, "Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD", *Chest*, vol. 121, no. 4, pp. 1058-1069. Ref ID: 966	Stable COPD
Murciano, D., Auclair, M. H., Pariente, R., & Aubier, M. 1989, "A randomised controlled trial of theophylline in patients with severe chronic obstructive pulmonary disease", *New England Journal of Medicine*, vol. 320, no. 23, pp. 1521-1525. Ref ID: 201	Stable COPD
All papers cross referenced to: McCrory, D. C., Brown, C., Gray, R. N., Goslin, R. E., MacIntyre, N. R., Kolimaga, J. T., Oddone, E. Z., & Matchar, D. 2001, *Management of acute exacerbations of chronic obstructive pulmonary disease.*, Agency for Healthcare Research and Quality., Rockville, MD, USA, 256. Ref ID: 1145	

Author / Title / Reference / Yr	Barr RG, Rowe BH, Camargo CA, Jr. Methylxanthines for exacerbations of chronic obstructive pulmonary disease. (Cochrane Review). *The Cochrane Library.Oxford: Update Software* 2003;**Issue 3**.
N=	N=4 RCTs. Total sample size N=172.
Design	Systematic Review with meta-analysis
Aim	To determine the benefit of methyl-xanthines compared to standard care for COPD exacerbations.
Operational Definition	Dolcetti - 15% or more improvement in FEV1 with salbutamol and prior diagnosis of COPD. Exacerbation not defined. Although all patients were described as having an exacerbation a cross over design was used. Rice - Prior spirometry of FEV1 <2SD below predicted and FEV1/FVC <60% and prior diagnosis of COPD. Exacerbation not defined. Seidenfield - ATS definition of chronic bronchitis. Wrenn - Not defined. Inclusion criteria state "asthma exacerbation or wheeze". No prior PFT data, likely to be some misclassification with asthma.
Population	Acute exacerbation COPD
Intervention	Methyl-xanthines (oral or intravenous)
Comparison	Placebo (with or without standard care)
Outcomes	FEV1 at 2hrs, PEFR at 2 hrs, hospitalisation or relapse at 48hrs after discharge, symptom scores and adverse events.
Characteristics	• Dolcetti – Mean age 58, gender 80% male. Experimental group 200mg doxofylline / 50ml saline over 15min. Control=placebo. • Rice – Mean age 65, gender 96% male. Experimental group IV aminophylline 0-6mg/kg load, 0.5mg/kg maintenance infusion for level of 72-94 umol/l (different in abstract 72-82). Control=placebo. • Seidenfield – Mean age 52, gender 100% male. Experimental group IV aminophylline 2.8-5.6 mg/kg over 1 hr. Control="D5W". • Wrenn – Mean age 62, gender 64% male. Experimental group IV aminophylline 5.6 mg/kg over 20 min, then 0.9mg/kg constant infusion. Control=placebo.
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1a

Results	**Pulmonary Function (3 trials)** Mean change in FEV1 at 2 hrs was non significant in methyl-xanthine and placebo groups (FEV1 WMD: -8ml; 95% CI: -85 to 69ml). One trial (Dolcetti 1988) which failed to include standard treatment demonstrated a significant treatment effect, however this was a cross over trial with a sample size of N=10. **Hospitalisation rate (One trial N=39)** Non significant reduction with methyl-xanthines (OR: 0.3; 95% CI:0.1 to 1.8). **Symptoms scores (2 trials)** There was significant heterogeneity (p=0.02) between the two trials that were aggregated. (Wrenn 1991 and Dolcetti 1988). The difference between the symptom scores in patients receiving methyl-xanthines compared to placebo not statistically significant (OR 5.6; 95%CI: 0.2 to 1.38). **Adverse Effects (3 trials)** The odds of nausea or vomiting were significantly higher for patients receiving a methyl-xanthine (OR: 4.8; 95% CI: 1.01 to 23) than those receiving placebo. Other effects were not recorded often enough to allow combination.
ID	859
Included references	Dolcetti 1988 (N=10), Rice 1982 (N=30), Seidenfield 1984 (N=52), Wrenn 1991 (N=39)

COPD Evidence Tables

The evidence tables are presented in section order.

The methodological quality of each paper was rated using the Scottish Intercollegiate Guidelines Network (SIGN) system (Scottish Intercollegiate Guidelines Network. SIGN 50 Guideline Developers Handbook, 2001; ID 19457):

++	All or most of the SIGN methodology checklist criteria were fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
+	Some of the criteria were fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
-	Few or no criteria were fulfilled. The conclusions of the study are thought likely or very likely to alter.

Chronic Obstructive Pulmonary Disease: Management of adults with Chronic Obstructive Pulmonary Disease in Primary and Secondary Care

Management of exacerbations of COPD
Respiratory Stimulants
Index

Author	Publication Date	ID
Bardsley, P. A., Tweney, J., Morgan, N., & Howard, P. 1991, "Oral almitrine in treatment of acute respiratory failure and cor pulmonale in patients with an exacerbation of chronic obstructive airways disease", *Thorax*, vol. 46, no. 7, pp. 493-498.	1991	1334
Greenstone M, Lasserson TJ, Doxapram for ventilatory failure due to exacerbations of chronic obstructive pulmonary disease (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd	2003	1290

Author / Title / Reference / Yr	Bardsley, P. A., Tweney, J., Morgan, N., & Howard, P. 1991, "Oral almitrine in treatment of acute respiratory failure and cor pulmonale in patients with an exacerbation of chronic obstructive airways disease", *Thorax*, vol. 46, no. 7, pp. 493-498. Ref ID: 1334
N=	N=23 Duration=3wks Location=UK Sites=Number of sites not stated
Research Design	Randomised, double blind placebo controlled trial
Aim	To examine the effect of oral almitrine in pts with acute on chronic respiratory failure and hypoxaemic cor pulmonale secondary to an exacerbation of COAD (chronic bronchitis and emphysema).
Operational Definition	Respiratory failure defined as PaO2 < 8.0 kPa / PaCO2 > 6.0 kPa Other inclusion criteria: Peripheral oedema / FEV1< 1.51 recorded either in the past or when clinically stable / FEV1/FVC <70%
Population	Chronic obstructive airways disease and hypoxaemic cor pulmonale admitted to hospital with acute exacerbation of ventilatory failure (asthma excluded)

Intervention	N=12 Oral almitrine 100 mg twice daily reducing to 50mg twice daily over 48 hrs in addition to conventional treatment
Comparison	N=11 Placebo in addition to conventional treatment
Outcomes	Arterial blood gas tensions, inspired oxygen requirement, symptoms and survival
Characteristics	Age range 51 to 82 years, mean age of almitrine group 65yrs whilst mean age of placebo group 72 years / Gender 14 men / 9 women / FEV1 0.21 – 1.11 L / Ventilatory failure on admission to hospital PaO2 3.2-6.7 kPa and PaCO2 6.2-10.0 kPa / Concomitant standard treatment and medication during the trial included oxygen, bronchodilators, chest physiotherapy, diuretics and antibiotics.
Results	N=17 completed the study **Mortality** 6 pts died. 5 pts receiving almitrine and one pt receiving placebo. The difference in death rate between the two groups was not statistically significant (p=0.09). **Arterial blood gas tension, and inspired O2 requirement** No significant differences between the two groups **FEV1 / FVC and respiratory rate** No significant differences between the two groups **Breathlessness and well being** No significant differences between the two groups
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b
NCC CC ID	1334

Author / Title / Reference / Yr	Greenstone M,. Lasserson T. Doxapram for ventilatory failure due to exacerbations of chronic obstructive pulmonary disease. (Cochrane Review). *The Cochrane Library.Chichester, UK: John Wiley & Sons, Ltd* 2003;**(4)**.
N=	RCTs x 4. N=176 people.
Research Design	Systematic review of RCTs
Aim	To assess the effects of doxapram on gas exchange and clinical outcomes in people with ventilatory failure due to acute exacerbations of COPD.
Operational Definition	See study characteristics below

Population	People with ventilatory failure (hypoxia and hypercapnia) due to exacerbations of COPD. Only spontaneously breathing subjects were included. (Excluded those who had received GA)
Intervention	Doxapram - Intravenous injection or infusion.
Comparison	None of the three papers compared doxapram with the same control. Moser (1973) compared doxapram with placebo. Angus (1996) compared doxapram with NIPPV. Edwards (1967) compared doxapram with four other respiratory stimulants: ethamivan, amiphenazole, prethcamide and nikethamide.
Outcomes	Blood gas data / Clinical effects including progression to endotracheal intubation and artificial ventilation / Mortality and length of hospital stay
Characteristics	**Edwards (1967)** – (random allocation & double blinded). N=32 pts in acute ventilatory failure (no other definition). Interventions include doxapram (3mg per kg per hr), ethamivan (12 mg per kg per hr), amiphenazole (3mg per kg per hr), prethcamide (12 mg per kg per hr), nikethamide (15 mg per kg per hr) infusions for four hrs. Outcomes included PCO2, O2 saturation, tidal volume, minute-volume, FEV1 at 4 hrs. Sputum vol, clinical response, proportional reduction of initial hypoxic and hypercapnic gap at 24 hrs. No operational definition of ventilatory failure (group mean PCO2> 50 mmHg). Small numbers in each group (N=7). Statistical comparisons were made on data obtained after 24 hrs and did not reflect the immediate changes in blood gases during the treatment period. **Moser (1973)** – (randomised and double blind). N=78 pts acute respiratory failure (PaCO2 > 50 mmHg, PaO2 < 50 mmHg). Underlying lung disease was not clearly documented, age range 21 to 78 yrs suggesting heterogeneous group. Intervention doxapram (2.8 mg per min) or placebo infusion for 2 hrs. Outcomes arbitrary improvement or failure (rise in PaCO2 of 10 mmHg or more, or pH decline, or intubation or tracheotomy). **Angus (1996)** – (un blinded RCT). N=17 (PaO2 <8kPa and PaCO2>6.7kPa). N=9 received NIPPV (mean age 64yrs) and N=8 received doxapram (mean age 62 yrs). IV doxapram infusion for 4hrs (4mg/min for 15 mins, 3mg/ min for 30 mins, 2mg/min for 60 mins, 1.5mg/min as maintenance). NIPPV using a pressure cycled machine set between 14-18cm H2O. Outcome = hrly arterial blood gases. No demographic table available. **Newman (2001)** – (random allocation, unblended parallel group study). N=49 pts (mean age 66.5yrs) and a diagnosis of acute COPD made by a consultant respiratory chest physician (PaCO2 greater than or equal to 6.6kPa, H+greater than or equal to 50 nmols/I). Intervention=Doxapram was administered via continuous intravenous infusion (45mgs per hour initially. This dosage was titrated). Outcomes=Arterial blood gas parameters measured at 1,4 and 24 hours. Length of hospital stay, treatment failures, mortality and intubation.
Results	Limited results presented here. Extensive results comparing Doxapram to placebo or other drugs fully detailed in original Cochrane systematic review by Greenstone 2002) • Doxapram compared to placebo in preventing blood gas deterioration (OR 0.38, 95% CI 0.14 to 1.02). Marginally superior to placebo however non significant. • Doxapram compared to NIPPV, best achieved PaO2 after treatment OR 0.800 (-0.729 to 2.329) although non significant, in favour of NIPPV. • Doxapram compared to NIPPV, best achieved PaCO2 after treatment OR 1.4 (-0.558 to 3.358) although non significant, in favour of NIPPV.

	• Doxapram compared to NIPPV, more deaths in the Doxapram group (OR 11.34, 95% CI, 1.00 to 128.03) • No numerical data have been entered for analyses for continuous data in the Newman (2001) study due to non-parametric distribution. Data on mortality and treatment failure have been restricted to narrative description. "Reviewers conclusion: Doxapram can improve blood gas exchange over the first few hours of treatment. Newer techniques such as non-invasive ventilation may prove to be more effective, although there is no randomised trial evidence to this effect".
SIGN Quality Rating	+ (For the critical appraisal of the systematic review) However the authors of the review highlight that the studies contained within the systematic review "were of variable quality"
Hierarchy of Evidence Grading	1a
NCC CC ID	1290

COPD Evidence Tables

The evidence tables are presented in section order.

The methodological quality of each paper was rated using the Scottish Intercollegiate Guidelines Network (SIGN) system (Scottish Intercollegiate Guidelines Network. SIGN 50 Guideline Developers Handbook, 2001; ID 19457):

++	All or most of the SIGN methodology checklist criteria were fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
+	Some of the criteria were fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
-	Few or no criteria were fulfilled. The conclusions of the study are thought likely or very likely to alter.

Chronic Obstructive Pulmonary Disease: Management of adults with Chronic Obstructive Pulmonary Disease in Primary and Secondary Care

Management of exacerbations of COPD
Non invasive ventilation (NIV) and COPD exacerbations
Index

Author	Publication Date	ID
Ram FSF, Lightowler JV, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease (Cochrane Review). In: The Cochrane Library, Issue 2, 2003. Oxford: Update Software.	2003	1485
Keenan, S. P., Kernerman, P. D., Cook, D. J., Martin, C. M., McCormack, D., & Sibbald, W. J. 1997, "Effect of noninvasive positive pressure ventilation on mortality in patients admitted with acute respiratory failure: a meta-analysis. [see comments.]", *Critical Care Medicine*, vol. 25, no. 10, pp. 1685-1692.	1997	887
Peter, J. V., Moran, J. L., Phillips-Hughes, J., & Warn, D. 2002, "Noninvasive ventilation in acute respiratory failure--a meta-analysis update", *Critical Care Medicine.*, vol. 30, no. 3, pp. 555-562.	2002	854
Conti, G., Antonelli, M., & Navalesi, P. 2002, "Noninvasive vs conventional mechanical ventilation in pts with COPD after failure of medical treatment in the ward; a randomised trial.", *Intensive Care Medicine*, vol. 28, pp. 1701-1707.	2002	1486
Thys, F., Roeseler, J., Reynaert, M., Liistro, G., & Rodenstein, D. O. 2002, "Non invasive	2002	1314

ventilation for acute respiratory failure: A prospective randomised placebo-controlled trial", *European Respiratory Journal*, vol. 20, no. 3, pp. 545-555.		Study terminated @ interim results
Plant, P. K., Owen, J. L., & Elliott, M. W. 2000, "Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial", *Lancet*, vol. 355, no. 9219, pp. 1931-1935.	2000	18
Keenan, S. P., Sinuff, T., Cook, D. J., Hill, N. S. (2003). Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation: A systematic review. Annals of Internal Medicine, 138, 861-870.	2003	19400

Author / Title / Reference / Yr	Ram FSF, Lightowler JVJ, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. (Cochrane Review). *The Cochrane Library.Oxford:Update Software* 2003;**Issue 3**. Ref ID: 1485
N=	N=8 studies. N=546 participants. Location=Hospital in patients. Geographic site=Russia, Turkey, Spain, France, Rome, USA & UK
Research Design	Systematic review and meta analysis of RCTs
Aim	To elicit the effectiveness of NPPV in the management of patients with respiratory failure due to an acute exacerbation of COPD.
Population	Patients with COPD. All patients had acute respiratory failure. All patients admitted into the study had to have a baseline admission PaCO2 > than 6kPa.
Intervention	NPPV via nasal or facemask in addition to usual medical care
Comparison	Usual medical care involving supplemental oxygen, antibiotics, bronchodilators, steroids, respiratory stimulants, diuretics, methylxanthines.
Outcomes	Primary: Treatment failure (the combination of mortality, intubation and intolerance to the allocated treatment) / Mortality during respiratory failure / Tracheal intubation. Secondary: Duration of hospital stay and ICU stay / Breathlessness scores / Complications / ABG 1hr post NPPV
Characteristics	Mean age 63 to 71yrs / Admission pH 7.26 to 7.34, PaCO2 7.7 to 10.79 kPa, PaO2 5.2 to 8.13 and FEV1 0.68 to 1.03 L. / Male to female ratio was 1.3:1
Results	NPPV compared to usual medical care decreased mortality, relative risk (RR) 0.41, 95%CI 0.26 to 0.64. Intubation compared to usual medical care decreased the need for intubation, RR 0.42, 95%CI 0.31 to 0.59. NPPV compared to usual medical care reduced treatment failure, RR 0.51, 95%CI 0.39 to 0.67. NPPV compared to usual medical care resulted in a rapid improvement within the first hour in pH, WMD 0.03, 95%CI 0.02 to 0.04, PaCO2, WMD –0.40 kPa, 95%CI –0.78 to –0.03 and respiratory rate WMD –3.08 bpm, 95%CI –4.26 to –1.89. Complications associated with NPPV compared to usual care were reduced in the NPPV group RR 0.32, 95%CI 0.18 to 0.56 Duration of hospital stay was reduced in the NPPV group compared to usual treatment WMD –3.24 days, 95%CI –4.42 to –2.06.
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1a
NCC CC ID	1485
Studies included	Avdeev 1998 (N=58), Barbe 1996 (N=24), Bott 1993 (N=60), Brochard 1995 N=85), Celikel 1998 (N=30), Dikensov

	2002 (N=34), Kramer 1995 (N=31), Plant 2000 (N=236).

Author / Title / Reference / Yr	Keenan, S. P., Kernerman, P. D., Cook, D. J., Martin, C. M., McCormack, D., & Sibbald, W. J. 1997, "Effect of noninvasive positive pressure ventilation on mortality in patients admitted with acute respiratory failure: a meta-analysis. [see comments.]", *Critical Care Medicine*, vol. 25, no. 10, pp. 1685-1692. Ref ID: 887
N=	N=7 RCTs, of the 7 trials, four included only COPD pts. Location= Frances, Greece, UK, USA.
Research Design	Meta analysis
Aim	To establish whether the addition of NPPV to standard therapy affects hospital mortality in pts admitted with acute respiratory failure. Secondary objectives were to determine a) effect of NPPV on intubation and b) whether the effect of NPPV was influenced by the underlying disease associated with acute respiratory failure (i.e. COPD pts vs. non-COPD pts).
Operational Definition	Operational definition of COPD not provided
Population	Pts with acute respiratory failure
Intervention	Non invasive positive pressure ventilation (volume cycled with nasal mask, pressure cycled with nasal mask and pressure support with nasal or face mask)
Comparison	Standard therapy (not specified)
Outcome	Mortality / Endotracheal intubation
Characteristics	Table provided in the paper for the inclusion criteria. PH, PaCO2, CaO2 given for all trials except Daskalopoulou which just states "COPD / cor pulmonale". PH <7.35 for Kramer, Brochard & Martin. pH <7.38 for Wysocki. PH not stated for Bott, Ahmed). Age parameters not provided. Asthma explicitly excluded for Wysocki & Brochard.
Results	**Mortality** Pooled data from 5 studies (Bott, Kramer, Wysocki, Brochard, Ahmed) demonstrated a statistically significant benefit in favour of non-invasive positive pressure ventilation (OR 0.29; 95%CI; 0.15 to 0.59). The COPD only trials (Bott, Brochard, Ahmed) demonstrated a strong survival advantage for NPPV (OR 0.22; 95% CI; 0.09 to 0.54). **Intubation** Pooled data from 5 studies (Kramer, Wysocki, Brochard, Daskalopoulou, Martin) demonstrated a strong treatment effect favouring NPPV (OR 0.20; 95%CI; 0.11 to 0.36). The COPD only trials (Kramer, Brochard, Daskaloupoulo) demonstrated a strong effect in favour of NPPV patients for a reduction in the need for subsequent need for endotracheal intubation (OR 0.12; 95%CI; 0.05 to 0.29).
SIGN Quality Rating	++
Hierarchy of Evidence	1a

Grading	
NCC CC ID	887
Studies Included	Bott et al 1993, Kramer et al 1995, Wysocki et al 1995, Brochard et al 1995, Ahmed et al 1992, Daskalopoulou 1993, Martin et al 1994

Author / Title / Reference / Yr	Peter, J. V., Moran, J. L., Phillips-Hughes, J., & Warn, D. 2002, "Noninvasive ventilation in acute respiratory failure--a meta-analysis update", *Critical Care Medicine.*, vol. 30, no. 3, pp. 555-562. Ref ID: 854
N=	RCT=15. N=793 Location=USA, UK, France, Italy, Spain, Turkey, Canada, Russia &Greece
Research Design	Meta analysis of RCTs
Aim	To address the role of NIV in reducing mortality in pts with acute respiratory failure
Operational Definition	COPD not defined
Population	Acute respiratory failure
Intervention	NIV (Pressure cycled ventilation was used in 14/15 trials. 1 study used volume-cycled ventilation.
Comparison	Standard medical therapy
Outcome	Mortality / Intubation / Hospital length of stay / Complication rates
Characteristics	Excluded asthma The criteria for acute respiratory failure were a combination of clinical state (moderate to severe dyspnoea, respiratory rate >24 breaths/minute, use of accessory muscles of respiration, paradoxic abdominal movement). Laboratory evidence of respiratory distress included pH <7.35 and / or PaO2 <60 mm Hg and / or PaCO2 >45. Age range not documented.
Results	**Mortality** Statistically significant reduction in mortality in all studies in favour of the NIV group compared to the standard therapy group. Risk Difference -0.08 (95%CI; -0.16 to –0.01). Statistically significant reduction in mortality in COPD sub group in favour of the NIV group compared to the standard therapy group. Risk Difference –0.13 (95%CI; -0.21 to –0.06) No statistically significant difference in the “mixed group” which constituted pneumonia, interstitial lung disease and other parenchymal processes and included COPD pts who had respiratory failure secondary to other cardiopulmonary disease processes). Risk Difference 0.00 (95%CI –0.13 to 0.13). **Intubation** NIV was associated with a statistically significant reduction in the need for mechanical ventilation across all groups compared to standard therapy. All studies - Risk difference –0.19 (95%CI; -0.26 to –0.09) COPD subgroup – Risk difference –0.18 (95%CI; -0.33 to –0.03).

	Mixed group – Risk difference –0.20 (95%CI; -0.32 to –0.05). **Hospital Length of Stay** Statistically significant reduction in the length of hospital stay in favour of the NIV group compared to the standard therapy group for All studies – Risk difference –2.74 (95%CI; -4.59 to –0.89) COPD subgroup – Risk difference –5.66 (95%CI –10.10 to –1.23) No statistically significant difference in the "mixed group". Risk difference –0.74 (95%CI –2.78 to 1.30). **Complications** Uneven reporting of complications was noted. No significant reduction in complications in the NIV group was demonstrated
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1a
NCC CC ID	854
Studies Included	Daskalopoulou 1993 (COPD), Bott 1993 (COPD), Kramer 1995 (Mixed), Wysocki 1995 (ARF), Brochard 1995 (COPD), Angus 1996 (COPD), Barbe 1996 (COPD), Celikel 1998 (Mixed), Avdev 1998 (COPD), Wood 1998 (Mixed), Confalonieri 1999 (Mixed), Lapinski 1999 (Mixed), Bardi 2000 (COPD), Martin 2000 (Mixed), Plant 2000 (COPD).

Author / Title / Reference / Yr	Conti, G., Antonelli, M., & Navalesi, P. 2002, "Non invasive vs conventional mechanical ventilation in pts with COPD after failure of medical treatment in the ward; a randomised trial.", *Intensive Care Medicine*, vol. 28, pp. 1701-1707. Ref ID: 1486
N=	N= 49. Location=Italy. Site=ICU (Eligible pts were transferred to ICU and randomly assigned). Follow-up at 1yr.
Research Design	Prospective randomised study
Aim	To compare the short and long term response to NPPV delivered via facemask vs conventional ventilation delivered via endotracheal intubation in COPD pts with acute respiratory failure failing to sustain the initial improvement with conventional medical therapy in the emergency ward.
Operational Definition	Acute respiratory failure (ARF) defined as respiratory acidosis with pH values <7.32, bicarbonate levels >30 mEq/l, hypoxaemia with PaO2 <45 while in room air, respiratory rate >30 rpm, history of worsening dyspnoea of <2wks duration. Pts were defined as requiring ventilatory support in ICU if they deteriorated despite medical treatment and met at least one of the following criteria: pH<7.20, SaO2 90% with a FIO2 of >0.35, resp rate <35 bpm or severe deterioration in mental status.

Population	COPD pts with acute respiratory failure
Intervention	Non invasive positive pressure ventilation (NPPV) N=23
Comparison	Conventional ventilation N=26
Outcome	Gas exchange / Length of ICU stay / number days on mechanical ventilation, overall complications / ICU mortality / hospital mortality
Characteristics	Average age 72yrs (range not given. Male / female ratio not given FEV1 % pred NVVP group 28 / control 33 L PH <7.2 Functional limitations due to COPD (measured by visual analogic scale) NPPV 4.6 / control 5.3
Results	**Short term** **Gas exchange -** Both NPPV & conventional ventilation significantly improved gas exchanges After 1 hr of ventilation 8/23 pts NPPV group and 17/26 in the conventional group had improved pH p=0.06. **ICU -** Both groups had similar lengths of stay, number of days on mechanical ventilation & overall complications **Mortality -** Both groups had similar ICU mortality / hospital mortality **Avoidance of intubation -** In the NPPV group, 48% (11/23) pts avoided intubation, survived, and had a shorter duration of ICU stay than intubated pts. **Morbidity** – Pts randomised to NPPV had a trend (non significant) toward a lower rate of ventilator associated pneumonia (3 vs 9; p=0.07) and severe sepsis or septic shock (6 vs 13; p=0.07). **1 yr post hospital discharge:** **Mortality –** No significant differences between the two groups. **Pts readmitted to hospital for acute exacerbation** – NPPV group 65% vs 100% p=0.016 **Pts requiring de novo permanent O2 supplementation** – NPPV 0% vs 36% p<0.01 **Total number of hospital & ICU admissions** – Similar OR 0.65, 95%CI; 0.12 to 3.42, p=0.41
SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	1486

Author / Title / Reference / Yr	Thys, F., Roeseler, J., Reynaert, M., Liistro, G., & Rodenstein, D. O. 2002, "Non invasive ventilation for acute respiratory failure: A prospective randomised placebo-controlled trial", *European Respiratory Journal*, vol. 20, no. 3, pp. 545-555. Ref ID: 1314
N=	N=20 (At the time of the first interim analysis of data from 20 pts, study was suspended due to the differences in the failure rate). Site=Emergency dept of an urban university teaching hospital. Location=Belgium
Research Design	Prospective, randomised placebo controlled single blind study
Aim	To clarify whether the known effects of NPPV in pts with respiratory failure are real or due to placebo effects and whether early application of NPPV in the emergency dept leads to rapid improvement of pts condition and outcome.
Operational Definition	Acute exacerbation of COPD defined as "acute respiratory distress in a cigarette smoker with a known history of long lasting dyspnoea on exertion with frequent exacerbations and cough, and mucus hyper production without symptoms of signs of other specific causes (absence of pneumothorax, pneumonia, pleural effusion, no reason to suspect an episode of pulmonary embolism)". "ARF defined as acute onset of moderate to severe dyspnoea, a respiratory rate of >30 bpm, hypoxaemia PaO2 <7.3kPa or need for O2 supplementation, respiratory acidosis pH <7.33".
Population	Severe acute respiratory failure secondary to an acute exacerbation of COPD or acute pulmonary oedema not improving under conventional medical therapy.
Intervention	N=10 Conventional medical therapy plus NPPV
Comparison	N=10 Conventional medical therapy plus placebo NPPV
Outcome	The need for endotracheal intubation in the NPPV arm and in the placebo arm after crossing over to active NPPV. Morbidity, length of stay, mortality & blood gases
Characteristics	11 males (NPPV group 7:3, placebo 4:6) / Smoking history (N=8 in NPPV group and N=4 in placebo) Mean age of pts 75yrs (range 52 to 89 yrs). / 40% (N=8) had acute pulmonary oedema, N=12 had COPD. No baseline FEV1 documented. / pH at baseline NPPV group 7.28 (7.1 to 7.39), pH at baseline placebo group 7.24 (7.08 to 7.43). Placebo group range indicates that study entry criteria of pH<7.33 invalidated).
Results	N=10 in active NPPV group improved and none needed intubation. N=10 in placebo NPPV required NPPV active ventilation, 3 of which required full intubation. No pts died in the first 24 hrs after admission. Three pts died afterwards, two in the NPPV group and one in the placebo group). Cause of death in the placebo group pt was end-stage cardiac failure.
SIGN Quality Rating	Study stopped at interim analysis
Hierarchy of Evidence Grading	1b
NCC CC ID	1314

Author / Title / Reference / Yr	Plant, P. K., Owen, J. L., & Elliott, M. W. 2000, "Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial", *Lancet*, vol. 355, no. 9219, pp. 1931-1935. Ref ID: 18
N=	N=236. Location=UK. Sites=14 hospitals.
Research Design	Prospective multicentre randomised controlled study. Setting For each recruiting hospital, one to three general medical or respiratory wards were identified as sites for NIV. 22/25 wards had no experience of NIV and only one was fully experience. None of the wards had previously used the study ventilator. None of the wards could invasively ventilate pts.
Aim	To find out whether NIV was feasible on the ward in non-specialist units and whether it was effective at reducing intubation and in hospital mortality compared with standard treatment.
Operational Definition	Acute exacerbation of COPD – clinical history, physical examination and CXR, were tachypnoeic with a respiratory rate o f>23 per min and had a pH 7.25 to 7.35 with a PaCO2 >6kPa on arrival to the general resp ward e.g. after initial treatment within the A&E dept and within a maximum of 12 hrs of admission. Pts with a pH below 7.25 were excluded as it was felt to be unethical to randomise these pts due to the known poor prognosis in this group.
Population	Pts admitted with mild to moderate acidosis due to an exacerbation of COPD.
Intervention	N=118 Standard treatment plus non invasive ventilation (NIV)
Comparison	N=118 Standard treatment Aminophylline and doxapram could be used at the discretion of the attending medical staff. Results demonstrated that the use of these drugs was not different between the two groups.
Outcome	Primary endpoint was intubation. Secondary outcomes arterial blood gases (ABG), spirometry, mobility, nutritional status, mask comfort, breathlessness, nursing workload
Characteristics	Two groups had similar characteristics on admission. Mean age 69 yrs (range not given) Gender M/F = Standard treatment 63/55, NIV 54/64 pH average 7.31 The median nurse: patient ratio was 1:11 (range 1:2.6 to 1:13) The mean amount of formal training given in the first 3/12 of opening a ward was 7.6 hours.
Results	**Intubation** Use of NIV significantly reduced the need for intubation 32/118 (27%) of standard group failed compared with 18/118 (15%) of NIV group p=0.02 **Mortality** In hospital mortality was reduced by NIV 24/118 (20%) died in the standard group compared with 12/118 (10%) in the

	NIV group (p=0.05) **PH, paCO2 and respiratory rate** Improved in both groups at 4 hrs (p<0.01). NIV led to a rapid improvement in pH in the first hr (p=0.02) and a greater fall in respiratory rate at 4hrs p=0.035. The duration of breathless ness was also reduced by NIV p=0.025. **Nursing work load** NIV led to a small increase in nursing time of only 26 minutes. The authors highlight that in a "low nurse to pt setting subsequent compliance could be expected to deteriorate compared with studies in ICU or with additional staff. However, the median compliance of 8 hr on day 1 and 7 hr on day 2 are similar to other trials".
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1b
NCC CC ID	18

Author / Title / Reference / Yr	Keenan, S. P., Sinuff, T., Cook, D. J., Hill, N. S. (2003). Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation: A systematic review. Annals of Internal Medicine, 138, 861-870.
N=	N=15 Studies, N=629 participants Site: 4 trials were multicenter, 11 were conducted in a single center. Location= 10 countries (2x UK; 1x Greece; 2x Italy; 1x France; 2x US; 1x Scotland; 1x Spain; 1x Russia; 2x Turkey; 1x Canada; 1x India)
Research Design	RCTs only
Aim	To assess the effect of NPPV on rate of endotracheal intubation, length of hospital stay, and in-hospital mortality rate in patients with an acute exacerbation of COPD and to determine the effect of exacerbation severity on these outcomes.
Operational Definition	No definition specified. Definitions between studies varies. 2x studies ATS definition; 5x studies not defined.
Population	Patients with acute exacerbations of COPD who required hospitilisation.
Intervention	Non invasive ventilation and standard therapy
Comparison	Standard therapy alone
Outcome	• Endotracheal intubation • Length of hospital stay • In-hospital mortality rate
Characteristics	No patient details provided.
Results	The addition of NPPV to standard care in patients with an acute exacerbation of COPD decreased the rate of endotracheal intubation (risk reduction, 28% [95% CI, 15% to 40%]); length of hospital stay (absolute reduction, 4.57

	days [CI, 2.30 to 6.83 days]), and in-hospital mortality rate (risk reduction, 10% [CI, 5% to 15%]). However, subgroup analysis showed that these beneficial effects occurred only in patients with severe exacerbations, not in those with milder exacerbations.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	Ia
Included Studies	Bott et al. (1993) N=50; Daskalopoutou et al., (1993) N=16; Servillo et al. (1994) N=10; Brochard et al. (1995) N=35; Kramer et al. (1995) N=23; Angus et al. (1996) N=17; Barbe et al. (1996) N=20; Avdeav et al. (1998) N=29; Celikel et al. (1998) N=20; Confalonieri et al. (1999) N=23; Martin et al. (2000) N23; Plant et al. (2000) N=236; Dikensoy et al. (2002) N=34; Keenan et al. (2001) N=52; Khilnani et al. (2002) N=40.
NCC CC ID	19400

Chronic Obstructive Pulmonary Disease: Management of adults with Chronic Obstructive Pulmonary Disease in Primary and Secondary Care

Management of exacerbations of COPD
Invasive ventilation and ITU care
Index

Author	Publication Date	ID
Esteban, A., Anzueto, A., Frutos, F., Alia, I., Brochard, L., Stewart, T. E., Benito, S., Epstein, S. K., Apezteguia, C., Nightingale, P., Arroliga, A. C., Tobin, M. J., & Mechanical Ventilation International Study Group 2002, "Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. [see comments.]", *JAMA*, vol. 287, no. 3, pp. 345-355.	2002	1307
Nevins, M. L. & Epstein, S. K. 2001, "Predictors of outcome for patients with COPD requiring invasive mechanical ventilation", *Chest*, vol. 119, no. 6, pp. 1840-1849.	2001	1488
Seneff, M. G., Wagner, D. P., Wagner, R. P., Zimmerman, J. E., & Knaus, W. A. 1995, "Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease", *JAMA*, vol. 274, no. 23, pp. 1852	1995	115
Rieves, R. D., Bass, D., Carter, R. R., Griffith, J. E., & Norman, J. R. 1993, "Severe COPD and acute respiratory failure. Correlates for survival at the time of tracheal intubation", *Chest*, vol. 104, no. 3, pp. 854-860.	1993	1487
Nava, S. N., Ambrosino, N., Clini, E., Prato, M., Orlando, G., Vitacca, M., Brigada, P., Fracchia,	1998	1311

C., Rubini, F. (1998). Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease: A randomized controlled trial. Ann Intern Med, 1998, 128, 721-728.		
Nava, S., Rubini, F., Zanotti, E., Ambrosino, N., Bruschi, C., Vitacca, M., Fracchia, C., Rampulla, C. (1994). Survival and prediction of successful ventilation for more than 21 days. Eur Respir J, 7, 1645-1652.	1994	1718

Author / Title / Reference / Yr	Esteban, A., Anzueto, A., Frutos, F., Alia, I., Brochard, L., Stewart, T. E., Benito, S., Epstein, S. K., Apezteguia, C., Nightingale, P., Arroliga, A. C., Tobin, M. J., & Mechanical Ventilation International Study Group 2002, "Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. [see comments.]", *JAMA*, vol. 287, no. 3, pp. 345-355. Ref ID: 1307
N=	N=15757 pts. N=361 ICUs. Sites=20 countries. Duration=28 days
Research Design	Descriptive case series (described by authors as "prospective cohort study design").
Aim	To determine the importance of factors influencing survival of mechanically ventilated pts. Study represents a heterogeneous group of mechanically ventilated pts, which prospectively evaluates the effect of more than 30 variables potentially related to mortality after controlling for the effect of confounding factors.
Operational Definition	COPD not operationally defined. Univariate and multivariate analysis of factors too numerous to list in this evidence table.
Population	Consecutive adult pts admitted to ICUs.
Exposure	Survivors - Pts who required mechanical ventilation for more than 12 consecutive hrs.
Non exposure	None survivors
Outcome	All cause mortality during intensive care stay.
Characteristics	Heterogeneous population (COPD constituted 10% of the pts mechanically ventilated 522/5183). Age (mean) 59yrs Gender (females) 1985/5183 (39%)
Results	5183/15757 (33%) received ventilation for an average of 6 days.

	Duration of ventilator support until the start of weaning, duration of weaning, length of stay in the ICU and hospital *Duration, Mean (SD)* — *Overall* — *COPD* — *ARDS* — *p value* Duration of mechanical ventilation — 5.9 (7.2) — 5.1 (5.3) — 8.8 (8.5) — <0.001 Duration of weaning — 4.2 (7.2) — 4.7 (7.8) — 5.0 (5.6) — 0.55 Length of stay in CIU — 11.2 (13.7) — 11.2 (10.6) — 24.5 (24.8) — 0.07 Length of stay in hospital — 22.5 (23.7) — 21.2 (17.7) — 24.5 (24.8) — 0.07 **Overall mortality rate in ICU:** 31% for the entire population 52% respiratory distress syndrome **22% in pts who received ventilation for an exacerbation of COPD.** 69% chance of survival in unselected pts receiving mechanical ventilation for >12 hours. **Main conditions independently associated with increased mortality were** The univariate analysis demonstrates that pts receiving mechanical ventilation due to acute decompensation of **COPD** had significantly lower mortality than pts receiving mechanical ventilation because of ARF of other aetiologies; COPD odds ratio (OR) 0.70; 95% CI 0.59 to 0.83; p=<0.001 compared to coma OR 1.31; 1.19 to 1.45; p<0.001 When mortality was adjusted for the effect of organ system failures and variables related to both the acute severity of illness and pt management, the mortality rate of **COPD** was not different from that of pts mechanically ventilated due to other aetiologies. The reason for the initiation of ventilation influences the outcome of ventilated pts. In a heterogeneous population of patients receiving mechanical ventilation, after adjusting for other variables, the only factors independently associated with decreased survival were coma, ARDS, and sepsis, and the only factor independently associated with increased survival was postoperative state. The main conditions independently associated with increased mortality were: 1. **Factors present at the start of mechanical ventilation** – coma OR 2.98; 95% CI 2.44 to 3.63; p<0.001. 2. **Factors related to patient management** – plateau airway pressure >35 cm H2O - OR 3.67; 95% CI 2.02 to 6.66; p<0.001 **3.** **Developments occurring over the course of mechanical ventilation** – ratio of PaO2 to fraction of inspired O2 <100 – OR 8.71; 95% CI 5.44 to 13.94; p<0.001.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	111

NCC CC ID	1307

Author / Title / Reference / Yr	Nevins, M. L. & Epstein, S. K. 2001, "Predictors of outcome for patients with COPD requiring invasive mechanical ventilation", *Chest*, vol. 119, no. 6, pp. 1840-1849. Ref ID: 1488
N=	N=166. Location USA. Site=Medical intensive care unit. Duration=4yr period, length of follow-up not specified.
Research Design	Described by authors as "retrospective cohort study using prospectively gathered data". Design type appears to be more of a descriptive case series.
Aim	A retrospective analysis was conducted on all pts with a history of COPD to identify the pt characteristics available at the time of hospital admission that predicted a poor outcome.
Operational Definition	Diagnosis of COPD determined by pre-morbid pulmonary function tests when available 76/166 pts. In the absence of PFT, clinical criteria (history with physical findings or evidence of hyperinflation on CXR) were used. ATS diagnostic definition used. Exacerbation of COPD was defined as an "increase in dyspnoea with or without cough and sputum production without concomitant evidence of pneumonia, CHF or other definable process". Severity of illness was measured using an acute physiology score (APS) and an APACHE 11 score measured 6 hrs after intubation. Criteria for intubation were not standardised (and NIV was infrequently used at the hospital during the study period).
Population	Patients with COPD who required mechanical ventilation for acute respiratory failure of various etiologies. (Entire cohort N=166) COPD exacerbations (N=39) Non exacerbations (N=127)
Exposure	Survivors - Pts exposed to invasive mechanical ventilation
Non exposure	None survivors
Outcome	**Primary outcomes -** Hospital death and place of discharge. **Secondary outcomes -** Death while receiving mechanical ventilation, duration of weaning, need for tracheotomy and disposition at time of discharge (e.g. spontaneous ventilation).
Characteristics	Age=67yrs (range not given) / Gender = 62% / Co-morbidity=42% / FEV1 L=1.24 +/-0.58 / FEV1 % predicted 48 +/-21
Results	**Duration of ventilation and hospital stay** Mean duration of ventilation was 9days (median 4 days) Mean duration of hospital stay was 22 days (median 14 days). **In hospital mortality rate** Entire cohort=28% (with 83% of those having died while still receiving ventilation).

	COPD exacerbation (without co-morbid illness)=12% COPD exacerbation=15% There were no significant differences between the survivors and non survivors regarding outpatient therapy (theophylline, inhaled or oral steroids, home O2) or smoking status. **Univariate mortality** There was a high mortality rate for those pts who: Required >72 hrs mechanical ventilation compared to those with <72hrs (37% vs 16%; p=<0.01) Those without previous episodes of mechanical ventilation (33% vs 11%; p<0.01) Those with a failed extubation attempt (36% vs 7%; p=0.0001) **Poor outcome predictors associated with a higher in hospital mortality** • Presence of APACHE 11 associated co morbidity (p=0.04) OR 2.87 95% CI 1.88 to 4.38 • Higher APS (p<0.001) (OR 1.10; 95% CI1.07 to 1.14) and APACHE 11 score when measured 6 hours after the onset of ventilation (p<0.001) • Presence of malignancy (p<0.0001) OR 4.04 95%CI 2.54 to 6.43 • Lower serum albumin level (p=0.01) • Lower haematocrit (p<0.001) • Higher FEV1/FVC (p=0.009) • Need for mechanical ventilation >72 hrs when compared to those pts who required <72 hr (37% vs 16% p=0.002) OR 2.57 95% CI 1.61 to 4.09 Authors conclude that "among variables available within the first 6 hrs of mechanical ventilation, the presence of co morbidity and a measure of the severity of the acute illness are predictors of in-hospital mortality among pts with COPD and acute respiratory failure. The occurrence of extubation failure or the need for mechanical ventilation beyond 72 hours also portends a worse prognosis".
SIGN Quality Rating	+
Hierarchy of Evidence Grading	111
NCC CC ID	1488

Author / Title / Reference / Yr	Seneff, M. G., Wagner, D. P., Wagner, R. P., Zimmerman, J. E., & Knaus, W. A. 1995, "Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease", *JAMA*, vol

	274, no. 23, pp. 1852. Ref ID 115
N=	N=362 admissions Duration=1 yr follow-up Location=USA Sites=42 ICUs
Research Design	Described by authors as "Prospective, multicentre, inception cohort study".
Aim	The purpose of the analysis was to describe hospital 90-day, 180 day and 1 year mortality for ICU admissions with acute exacerbation of COPD and to examine how individual prognostic variables influence these outcomes.
Operational Definition	No operational definitions for COPD / severity of COPD / or exacerbation given.
Population	Acute exacerbations of COPD (non operative pts whose primary reason for ICU admission was an acute exacerbation). 362 pts with COPD exacerbations were selected from the Acute Physiology Health Evaluation (APACHE) 111 database of 17440 ICU admissions
Exposure	Survivors Admission to ICU N=170 ventilated N=192 not ventilated
Non exposure	Non survivors
Outcomes	Mortality at 90 days, 180 days and 1 yr
Characteristics	Mean age 66yrs / Gender 44% female / Race 88% white / moderate to severe functional limits at baseline 45% / Mean APACHE 111 score 57 / mean APS 44
Results	**% Ventilated** On ICU day 1, 170/362 (47%) of COPD admissions for acute exacerbation of COPD were mechanically ventilated. ICU mortality 16% for those pts ventilated and 4% for pts not ventilated Hospital mortality 32% for pts ventilated and 17% for those not ventilated. Mechanical ventilation on day 1 was not an independent predictor of hospital or long term mortality The increase hospital mortality for ventilated pts was explained by a higher mean APS 50% in ventilated and 38% in non-ventilated group. **(Other data presented in paper, as per below, is <u>not</u> ventilator / non ventilator stratified)** **Mortality** 24% at hospital discharge 9% ICU mortality **Mortality and age** Hospital mortality for pts aged > 65 yrs was 33% (33% quoted in main text but 30% quoted in abstract) Hospital mortality for pts aged < 65 yrs was 10% **Mortality aged >65yrs** 216/362 (60%) were aged > 65yrs and survival status up to 1 yr after hospital discharge was available for 167 pts.

	Overall mortality in this group constituted: 30% at hospital discharge 42% at 90 days (abstract quotes 41%) 48% at 180 days (abstract quotes 47%) 59% at 1 yr **Hospital mortality and important predictors in pts N=167 aged>65yrs** (Multiple regression analysis) p<0.05 • Age, severity of respiratory and non-respiratory organ system dysfunction and hospital length of stay before ICU admission were all variables associated with hospital mortality. (Numerical values not given, bar chart parameters of % of explanatory power only available). • Development of non-respiratory organ system dysfunction was the **major** predictor of hospital mortality (60% of total explanatory power) and 180 day outcomes (54% of explanatory power). • Respiratory physiological variables (respiratory rate, serum pH, PaCO2, PaO2 and alveolar-arterial difference in partial pressure of O2 indicative of advanced dysfunction were more **strongly associated** with 180 day mortality rates (22% of explanatory power) than hospital death rates (4% of explanatory power). • After controlling for severity of illness, mechanical ventilation at ICU admission was **not associated** with either hospital mortality or subsequent survival (levels not given). • Function limits were not significant predictors of mortality at hospital discharge or 180 days, but were significantly predictive of 1 year mortality (69% for pts with functional limits vs 50% for pts without functional limits) p=0.01
SIGN Quality Rating	+
Hierarchy of Evidence Grading	111
NCC CC ID	115

Author / Title / Reference / Yr	Rieves, R. D., Bass, D., Carter, R. R., Griffith, J. E., & Norman, J. R. 1993, "Severe COPD and acute respiratory failure. Correlates for survival at the time of tracheal intubation", *Chest*, vol. 104, no. 3, pp. 854-860. Ref ID: 1487
N=	N=33. Location=Veterans Affairs Medical Centre, medical intensive care unit (MICU) USA. Sites=1. Duration=time of tracheal intubation
Research Design	Prospectively data collection cohort study Design appears to be more of a case series
Aim	1. Identification of clinical findings present at the time of tracheal intubation that were associated with successful weaning from mechanical ventilation.

	2. Identification of clinically objective and useful findings that may predict successful weaning and short-term survival.
Operational Definition	• Severe COPD was defined as a baseline FEV1 less than 1 L among pts with compatible history and physical findings of COPD. • Criteria for study inclusion were prior spirometry confirmation of fixed airways obstruction during a period of clinical stability and the development of ARF requiring endotracheal intubation and mechanical ventilation.
Population	N=33 men with severe COPD (39 episodes of acute respiratory failure requiring ventilation). Baseline FEV1 <1 L N=19 men with baseline FEV1 >1 L
Exposure	Survivors
Non Exposure	Non survivors
Outcome	Correlates for survival
Characteristics	All pts with ARF related to trauma or surgery were excluded. Gender 100% male Average age 66yrs (FEV1 < 1L) and 70 yrs for (FEV1 >1L)
Results	**Mortality rate** Pts with FEV1 <1L - 44% mortality rate Pts with FEV1 >1L - 42% mortality rate **Pts with FEV1 <1L** Higher serum albumin level and absence of pulmonary infiltrates on CXR distinguished survivors (weaned from ventilation for 72hrs) from non-survivors (died while undergoing ventilation of within 72 hr of weaning). The absence of infiltrates on CXR was the most significant correlate for survival ($p<0.001$). A higher serum albumin level was of lesser significance ($p=0.096$) Predictive modelling using these two covariates demonstrated a sensitivity of 88% and a specificity of 91%. **Pts with FEV1 >1L** Unlike pts with severe COPD, the presence or absence of pulmonary infiltrates on CXR was not correlated with survival in pts with milder COPD. Non-survivors were older, had lower haematocrits and were less alert at the onset of acute respiratory failure. Multivariate analysis of the covariates could not be performed due to the small sample size. **Combining data from mild and severe COPD** The extent of baseline airways obstruction alone was not statistically correlated with short-term survival in either cohort. Predictive modelling analysis of all data demonstrated an interaction of the baseline FEV1 and the presence or absence of pulmonary infiltrates as a predictor of short-term mortality. The relative risk of non-survival (mortality risk ratio MRR) for pts with infiltrates as compared with those pts without infiltrates demonstrated a sensitivity of 84% and a specificity of 79% when applied to all the data. **FEV1 MRR 95% CI** 0.40 147 16 to 1380

	0.60	103	14 to 779
	0.80	72	11 to 459
	1.00	50	9 to 286
	1.20	35	7 to 190
	1.40	23	4 to 127
	1.60	17	3 to 105
	1.80	12	2 to 86
SIGN Quality Rating	+		
Hierarchy of Evidence Grading	111		
NCC CC ID	1487		

Author / Title / Reference / Yr	Nava, S. N., Ambrosino, N., Clini, E., Prato, M., Orlando, G., Vitacca, M., Brigada, P., Fracchia, C., Rubini, F. (1998). Non invasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease: A randomized controlled trial. Ann Intern Med, 1998, 128, 721-728.
N=	N=50 participants Location= Montescano, Gussago, Novi Ligure- Italy Sites=3 respiratory ICUs.
Research Design	Two group, parallel, multicenter RCT
Aim	To determine whether non invasive ventilation improves the outcome of weaning from invasive mechanical ventilation.
Operational Definition	COPD not defined. Acute relapse was defined as respiratory acidosis (ph<7.33 while breathing room air); elevated bicarbonate levels; hypoxemia (PaO_2 <45mmHg while breathing room air); and severe dyspnoea in the absence of an objectively documented cause, such as pneumonia or 1 of 11 nonoperative respiratory diagnoses (excluding COPD) found in the Acute Physiology, Age, and Chronic Health Evaluation (APACHE) III.
Population	Intubated patients with chronic obstructive pulmonary disease and acute hypercapnic respiratory failure. T-piece weaning trial attempted 48 hours after intubation. If this failed two methods of weaning were compared.
Intervention	Non invasive pressure support ventilation by face mask group= N=25
Comparison	Invasive pressure support by ET tube ventilation group= N=25
Outcome	• Arterial blood gases • Duration of mechanical ventilation • Time in the intensive care unit • Occurrence of nosocomial pneumonia • Survival at 60 days
Characteristics	• Mean age= non-invasive/invasive 68.7yrs/67.0yrs • FEV1 ml= non-invasive/invasive 501/525 • % predicted FEV1= non-invasive/invasive 16.9/17.4 • Vital capacity ml= non-invasive/invasive 992/1089 • % predicted vital capacity= non-invasive/invasive 28.0/29.2 • FEV1 vital capacity role= 50.7/49.2 • Patients were excluded if they had severe concomitant diseases.
Results	At 60 days, 88% who were ventilated non-invasively were successfully weaned compared with 68% who were ventilated invasively. The mean duration of mechanical ventilation was 16.6 days for the invasive ventilation group and 10.2 days for the non-invasive ventilation group (p=0.021). • Arterial blood gases

	Invasive ventilation significantly improved blood gas values ($p<0.001$) in the two groups of patients at admission. • Duration of mechanical ventilation Patients who were weaned by using the non-invasive technique spent significantly fewer days receiving mechanical ventilation (invasive technique- 16.6 days and non-invasive technique- 10.2 days; p=0.021). • Time in the intensive care unit Patients who were weaned by using the non-invasive technique (compared to those weaned by using the invasive technique) spent significantly fewer days in the intensive care unit (Invasive technique- 24.0 days and non-invasive technique- 15.1 days; p=0.005). • Occurrence of nosocomial pneumonia 28% of patients in the invasive ventilation group and no patients in the non-invasive ventilation group developed nosocomial pneumonia. • Survival at 60 days Mortality rate at 60 days was significantly higher in the invasive ventilation group compared to the non- invasive ventilation group (92% and 72%; p=0.009). • Lung function at discharge At discharge from the intensive care unit, patients in the non invasive ventilation group and the invasive ventilation group were similar for FEV1 (510 mL or 17.1% of the predicted value and 537 mL or 17.8% of the predicted value), vital capacity (901 mL or 27.3% of the predicted value and 937 mL or 29.2% of the predicted value) and the ratio of the two measures (56% and 58%).
SIGN Quality Rating	+
Hierarchy of Evidence Grading	Ib
NCC CC ID	1311

Author / Title / Reference / Yr	Nava, S., Rubini, F., Zanotti, E., Ambrosino, N., Bruschi, C., Vitacca, M., Fracchia, C., Rampulla, C. (1994). Survival and prediction of successful ventilation for more than 21 days. Eur Respir J, 7, 1645-1652.
N=	Total N=42 participants Location= The Intermediate Intensive Care Unit (IICU) of Montescano Rehabilitation Center in Italy. Sites=1
Research Design	Prospective cohort study
Aim	1) To describe the outcome and long term survival of COPD patients ventilated for more than 21 days; and 2) To identify simple parameters, recorded in a phase of clinical stability, which would be useful to predict whether or not these patients will eventually be disconnected from the ventilator.

Operational Definition	COPD was defined using the American Thoracic Society criteria
Population	COPD patients requiring prolonged MV (more than 21 days) after an episode of acute respiratory failure requiring admission to an immediate intensive care unit.
Intervention	Successfully weaned group N=23
Comparison	Non-successfully weaned group N=19
Outcome	Outcomes assessed: • Predictive factors for the weaning process. • Survival of the COPD patients • Predictive factors for survival All variables measured were recorded a few days after IICU admission (from 5-10 days), whilst the patients were still ventilated but in a phase of clinical stability and included: • Anthropometric data • Arterial blood gases • Serological status • Nutritional status • Pulmonary function test • Number of pulmonary exacerbations
Characteristics	**Age** Successfully/unsuccessfully weaned group= 67yrs/66yrs **PaO_2 kPa** Successfully/unsuccessfully weaned group= 6.8/5.8 **$PaCO_2$ kPa** Successfully/unsuccessfully weaned group= 7.0/9.1 **$PaO_2/F10_2$ on MV** Successfully/unsuccessfully weaned group= 30.8/26.9 **$PaCO_2/F10_2$ on MV** Successfully/unsuccessfully weaned group= 6.9/7.4 **FEV1 % pred** Successfully/unsuccessfully weaned group= 25/21 **FEV1/FVC %** Successfully/unsuccessfully weaned group= 45/40 **Pulmonary exacerbations N** Successfully/unsuccessfully weaned group= 1.2/1.9 **Cor pulmonale on ECG %** Successfully/unsuccessfully weaned group=46.7/49.0 **Duration of MV to weaning days** Successfully/unsuccessfully weaned group=44.
Results	• <u>Predictive factors for the weaning process</u> Only six of the variables considered ($Paco_2$ kPa, Pao_2 kPa, MIP cmH_2O, P_{01} cmH_2O, flVt breaths.min^{-1}/l, serum protein gl^{-1}) were important in allowing a distinction between patients that were successfully weaned or not. The best discriminate equation included $Paco_2$ (75% sensitivity; 72% specificity; 73% predictive value) and MIP (76% sensitivity; 78% specificity; 81% predictive value) correctly predicting the outcome in 84% of the patients. • <u>Survival of the COPD patients</u> *At 2 yrs, 68% of group A patients and 22% of Group B were still alive ($p<0.01$); the cumulative rate of survival was*

	40%. • Predictive factors for survival The authors were unable to predict the survival rate. The best equation including $Paco_2$, Pao_2, age and serum protein level, could correctly predict the survival at one year in only 52% of the patients.
SIGN Quality Rating	-
Hierarchy of Evidence Grading	IIa
NCC CC ID	1718

COPD Evidence Tables

The evidence tables are presented in section order.

The methodological quality of each paper was rated using the Scottish Intercollegiate Guidelines Network (SIGN) system (Scottish Intercollegiate Guidelines Network. SIGN 50 Guideline Developers Handbook, 2001; ID 19457):

++	All or most of the SIGN methodology checklist criteria were fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.
+	Some of the criteria were fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.
-	Few or no criteria were fulfilled. The conclusions of the study are thought likely or very likely to alter.

Chronic Obstructive Pulmonary Disease: Management of adults with Chronic Obstructive Pulmonary Disease in Primary and Secondary Care

Management of exacerbations of COPD
Respiratory Physiotherapy and exacerbations
Index

Author	Publication Date	ID
Jones AP, Rowe BH. Bronchopulmonary hygiene physical therapy for chronic obstructive pulmonary disease and bronchiectasis (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2003. Oxford: Update Software.	2002	1345
Bellone, A., Spagnolatti, L., Massobrio, M., Bellei, E., Vinciguerra, R., Barbieri, A., Iori, E., Bendinelli, S., & Nava, S. 2002, "Short-term effects of expiration under positive pressure in patients with acute exacerbation of chronic obstructive pulmonary disease and mild acidosis requiring non-invasive positive pressure ventilation", *Intensive Care Medicine*, vol. 28, no. 5, pp. 581-585.	2002	1342
McCrory, D. C., Brown, C., Gray, R. N., Goslin, R. E., MacIntyre, N. R., Kolimaga, J. T., Oddone, E. Z., & Matchar, D. 2001, *Management of acute exacerbations of chronic obstructive pulmonary disease.*, Agency for Healthcare Research and Quality., Rockville, MD, USA, 256.	2001	1145
Bellone, A., Lascioli, R., Raschi, S., Guzzi, L., & Adone, R. 2000, "Chest physical therapy in patients with acute exacerbation of chronic bronchitis: Effectiveness of three methods", *Archives of Physical Medicine & Rehabilitation*, vol. 81, no. 5, pp. 558-560.	2000	1338

Wollmer, P., Ursing, K., Midgren, B., & Eriksson, L. 1985, "Inefficiency of chest percussion in the physical therapy of chronic bronchitis", *European Journal of Respiratory Diseases*, vol. 66, no. 4, pp. 233-239.	1985	1344
Newton, D. A. & Bevans, H. G. 1978, "Physiotherapy and intermittent positive-pressure ventilation of chronic bronchitis", *British Medical Journal.*, vol. 2, no. 6151, pp. 1525-1528.	1978	1341
Brown, P. A., Manfreda, J., McCarthy, D. S., MacDonald, S. (1987).The effect of mechanical vibration in patients with acute exacerbations of chronic obstructive pulmonary disease. Physiotherapy Canada, 39, 6, 371-374.	1987	1497

Author / Title / Reference / Yr	Jones AP,. Rowe BH. Bronchopulmonary hygiene physical therapy for chronic obstructive pulmonary disease and bronchiectasis (Cochrane Review). *The Cochrane Library.Oxford: Update Software* 2003;**Issue 3**. Ref ID 1345
N=	N=7 RCTs. N=126 people. Locations=Canada, UK, USA and Sweden
Research Design	Systematic Review and meta analysis (includes RCTs with or without blinding).
Aim	To assess the effects of bronchial hygiene physical therapy in people with COPD and bronchiectasis.
Operational Definition	Operational definition of COPD not given. Exacerbation definition not given. Severity of COPD not specified.
Population	Stable and exacerbation COPD population mixed. Bronchiectasis. Cystic fibrosis (N=4 patients). Asthma (N=1 pt) In patients and out patients.
Intervention	Manual interventions such as postural drainage, chest percussion, vibration, chest shaking, directed coughing or forced exhalation technique.
Comparison	No intervention, placebo, coughing, mechanical interventions such as positive pressure and mechanical vibration.
Outcome	Pulmonary function, blood gases, pulmonary clearance (sputum production, radio aerosol clearance), adverse reactions, symptoms (dyspnoea), general outcomes (such as resolution of CXR, mortality, length of hospital stay.
Characteristics	Age range: Bateman (1981) age unspecified, May (1979) 37 to 83 years, mean 59yrs, Mohsenifar (1985) 47 to 83 yrs, mean 69yrs, Newton (1978) age unspecified, Oldenburg (1979) 55 to 70 yrs, mean 62 yrs, Olseni (1994) age mean 57

	yrs, Sutton (1983) 19 to 60, mean 41 yrs.
Results	Authors state "Trials were small and not generally of high quality. The results could not be combined as trials addressed different pt groups and outcomes. In most comparisons, bronchial hygiene physical therapy produced no significant effects on pulmonary function, apart from clearing sputum in COPD and bronchiectasis". The only trial that had a situation specific population of acute exacerbations of COPD was Newton (1978). This trial has been critically appraised separately and an Evidence Table compiled, see ID 1341.
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1a
Studies included	Bateman 1981 (N=6, stable disease), May 1979 (N=35, stable disease), Mohsenifar 1985 (N=20, stable disease), Newton 1978 (N=33, exacerbations), Oldenburg 1979 (N=8, chronic bronchitis), Olseni 1994 (N=14, outpatients with chronic bronchitis), Sutton 1983 (N=10, bronchiectasis, cystic fibrosis, asthma).
Studies excluded	Agoston (1968), Ambrosino (1981), Anthonisen (1964), Belcastro (1984), Boksha (1989), Boye 1994), Castillo (1985), Cegla (1993 & 1994), Christensen (1990 & 1991), Clark (1986), Conway (1992), Craven (1974), Edenbrandt (1990), Feldman (1979), Foglio (1992), Gallon (1991), Hansen (1990), Hasani (1991), Kraszko (1973), Lorin (1971), Luttman (1994), Marcq (1981), Mazzoco (1985), Nichols (1970), Pavia (1976), Peterson (1976), Pryor (1979), Rivington (1984), Sutton (1985), Toevs (1984), Tonnesen (1982), Vandschans (1986 & 1990), Vanhengstum (1988 & 1991), Wollmer (1985).
NCC CC ID	1345

Author / Title / Reference / Yr	Bellone, A., Spagnolatti, L., Massobrio, M., Bellei, E., Vinciguerra, R., Barbieri, A., Iori, E., Bendinelli, S., & Nava, S. 2002, "Short-term effects of expiration under positive pressure in patients with acute exacerbation of chronic obstructive pulmonary disease and mild acidosis requiring non-invasive positive pressure ventilation", *Intensive Care Medicine*, vol. 28, no. 5, pp. 581-585. Ref ID: 1342
N=	N=27 Site=Respiratory intensive care unit. Location= Italy Duration=2/12
Research Design	Prospective, randomised, controlled study.
Aim	To investigate the feasibility and the efficacy of expiration under positive pressure as a chest physiotherapy
Operational Definition	ATS criteria were used to define COPD Acute exacerbation of COPD was defined on the basis of the clinical history, physical examination and CXR
Population	Pts with acute exacerbations of COPD
Intervention	N=13 PEP mask plus assisted coughing. PEP physiotherapy consisted of three daily sessions of 30-40 min each for the first 3/7 from the beginning of NIPPV. After 1 hr from the beginning of NIPPV, pts were randomly allocated to PEP mask plus assisted coughing or assisted coughing alone (as per the comparison group).
Comparison	N=14 Assisted coughing
Outcome	Primary – Compare total sputum wet weight and to assess the feasibility of the PEP mask. Secondary – Time required for weaning pts from NIPPV / treatment failure expressed as mortality within 2/12 after discharge from the ICU.
Characteristics	Mean age 65yrs / Gender 63% male / Mean APACHE 11= 17 / Blood gases pH between 7.25 to 7.35 (Mean 7.33) / PaO2 6.9 PaCO2 9.8kPa / Maintenance of SaO2 >85% / FEV1 intervention group 935(m), control group 858 (m) / FEV1/VC % 39
Results	**Sputum production** Significantly higher in the PEP mask plus assisted coughing group (10g) compared to the control group (5g) of assisted coughing alone ($p<0.01$). **Mask comfort** Only two pts referred to discomfort but did not stop treatment **Weaning time from NIPPV** Significantly lower in the intervention group (5 days) compared to the control group (7 days) ($p<0.01$) **Mortality** No significant differences **End tracheal intubation** No significant differences

SIGN Quality Rating	+
Hierarchy of Evidence Grading	1b
NCC CC ID	1342

Author / Title / Reference / Yr	McCrory, D. C., Brown, C., Gray, R. N., Goslin, R. E., MacIntyre, N. R., Kolimaga, J. T., Oddone, E. Z., & Matchar, D. 2001, *Management of acute exacerbations of chronic obstructive pulmonary disease.*, Agency for Healthcare Research and Quality., Rockville, MD, USA, 256. Ref ID: 1145
N=	N=3 RCTs
Design	Systematic Review / Technology Assessment
Aim	To assess the efficacy of physical therapy for pts with acute exacerbations of COPD
Population	Acute exacerbations of COPD
Intervention and Comparisons	Direct cut and paste quote: • "Three RCTs of chest physiotherapy were included (Newton and Bevans, 1978; Petersen, Esmann, Høncke, et al., 1967; Wollmer, Ursing, Midgren, et al., 1985) . • A fourth study in a group of patients with acute exacerbation of COPD did not report suitable outcome data (only blood gases, temperature, and sputum production) (Anthonisen, Riis, and Søgaard Andersen, 1964). • Three other controlled trials of various physical therapy modalities were conducted in patients who were not in acute exacerbation (Maloney, Fernandez, and Hudgel, 1981; van Hengstum, Festen, Beurskens, et al., 1990; van Hengstum, Festen, Beurskens, et al., 1991) or who were in post exacerbation (Kirsten, Taube, Lehnigk, et al., 1998)."
SIGN Quality Rating	++
Hierarchy of Evidence Grading	1a
Results	Direct cut and paste quote: • "Efficacy - None of the included trials reported any benefit over control for ventilatory function (FEV_1 or FVC). One trial described a significantly lower FEV_1 in patients who received chest percussion therapy compared with control (Wollmer, Ursing, Midgren, et al., 1985). A similar transient decrease in FEV_1 following chest percussion was previously described in an uncontrolled study (Campbell, O'Connell, and Wilson, 1975). • Adverse effects. Other than the data on short-term decrease in FEV_1 immediately following chest physiotherapy, no other information on adverse effects was provided. • Summary. Available studies of chest physiotherapy fail to show any improvement in short-term ventilatory

	function for patients with acute exacerbation of COPD.”
ID	1145

Author / Title / Reference / Yr	Bellone, A., Lascioli, R., Raschi, S., Guzzi, L., & Adone, R. 2000, "Chest physical therapy in patients with acute exacerbation of chronic bronchitis: Effectiveness of three methods", *Archives of Physical Medicine & Rehabilitation*, vol. 81, no. 5, pp. 558-560. Ref ID: 1338
N=	N=10. Site=Clinical ward. Location=Italy. Duration=1 hour
Research Design	Prospective, randomised study (no control hence quasi experimental)
Aim	To compare the short term effects of postural drainage (PD), oscillating positive expiratory pressure (using the FLUTTER device), and expiration with the glottis open in the lateral posture (ELTGOL)
Operational Definition	Chronic bronchitis defined as cough daily and expectoration for at least 3/12 for the last 2 yrs, who were known to produce more than 30ml sputum per day. Acute exacerbation was defined as the appearance of mucopurulent or purulent sputum and increasing cough, and one or more of the following symptoms: temperature of >38°C, general malaise, increased dyspnoea, increased mucus production, or thickness or increased difficulty in expectoration.
Population	Pts with an acute exacerbation of chronic bronchitis.
Intervention	Each pt received FLUTTER, ELTGOL and PD. Each pt received each treatment by the same respiratory therapist at the same time of day on separate days in random order.
Comparison	No control
Outcome	O2 saturation, pulmonary function and sputum production
Characteristics	Age range 47 to 64 yrs (mean 58 yrs) / No other demographics available.
Results	**O2 saturation -** No significant difference in SaO2 **FEV1 -** No significant difference in FEV1 during treatments **Sputum production** 30 minutes after treatment: FLUTTER 9.5g to 15.0g, p<0.01 / ELTGOL 10.3g to 17.0g, p<0.01 / PD 9.3g to 15.5g, p<0.01 1 hour after treatment: FLUTTER 15g to 19g, p<0.01 / ELTGOL 17g to 21g, p<0.02 / PD 16g to 17g, not significant.
SIGN Quality Rating	-
Hierarchy of Evidence Grading	11b
NCC CC ID	1338

Author / Title / Reference / Yr	Wollmer, P., Ursing, K., Midgren, B., & Eriksson, L. 1985, "Inefficiency of chest percussion in the physical therapy of chronic bronchitis", *European Journal of Respiratory Diseases*, vol. 66, no. 4, pp. 233-239. Ref ID: 1344
N=	N=10 Site=Not specified. Location=Sweden. Duration=2 days.
Research Design	Randomised, cross over study.
Aim	To evaluate the effect of chest percussion by comparing chest physiotherapy (postural drainage, instructed coughing) with and without chest percussion.
Operational Definition	COPD not defined. Exacerbation not defined. Severity not defined.
Population	Pts recovering from an acute exacerbation of chronic bronchitis. All pts had been admitted to hospital because of an acute exacerbation of bronchitis and were studied after a few days of treatment.
Intervention	Chest percussion and (postural drainage, instructed coughing) vs no percussion. Postural drainage = 5 mins in each of 3 positions (supine, right and left decubitus). Chest percussion administered by physio and continued throughout the postural drainage. Each period of postural drainage was followed by instructed coughing
Comparison	All pts were studied twice on consecutive days (no standard control group).
Outcome	Spirometric parameters, deposition of inhaled particles, O2 saturation and clearance of inhaled radio labelled particles.
Characteristics	Mean age 72 yrs 6 men and 4 women FEV1 42 +/- 16% of predicted. Concomitant medication bronchodilator drugs and some pts were receiving steroids (no further details given).
Results	**Percussion** Physiotherapy including chest percussion was associated with a statistically significant decrease in FEV1, percussion omitted –0.5 +/- 8.0 vs percussion included –7.3 +/- 6.5; $p<0.01$. Time parameter for when this was measured post treatment is not documented. **Deposition or clearance of inhaled radio labelled particles** -There was no difference between the two groups. **O2 saturation** - No significant differences
SIGN Quality Rating	-
Hierarchy of Evidence Grading	11b
NCC CC ID	1344

Author / Title / Reference / Yr	Newton, D. A. & Bevans, H. G. 1978, "Physiotherapy and intermittent positive-pressure ventilation of chronic bronchitis", *British Medical Journal.*, vol. 2, no. 6151, pp. 1525-1528. Ref ID: 1341
N=	N=79. Site=Pts admitted to one UK hospital, no other site specified. Location=UK. Duration= Up to 3/12
Research Design	Randomised controlled trial
Aim	Not specified
Operational Definition	An acute exacerbation of bronchitis was defined as an increase in cough, phlegm or breathlessness for >24hrs occurring in a pt with chronic bronchitis. No other definitions given.
Population	Pts admitted to hospital with exacerbation of chronic bronchitis alone or in association with cor pulmonale, pneumonia or respiratory failure. Groups stratified pre randomisation for: Men with hypoxia (Group 1) N=27 Men without hypoxia (Group 2) N=36 Women (Group 3) N=16
Intervention	Standard drug treatment plus physiotherapy and intermittent positive pressure ventilation (IPPV). Physiotherapy was given 3 times daily for 10-15 minutes “in a standard fashion by means of conventional methods” which is not defined. IPPV was given at 9a.m. by a physiotherapist and at 14:00 & 18:00 by a nurse. “BIRD ventilation”.
Comparison	Standard drug treatment
Outcome	FEV1 / Blood gases / Sputum volume / morbidity and mortality during hospital stay and within 3/12 of discharge / duration of hospital stay
Characteristics	Pts were excluded if they had significant co-morbidity / simple bronchitis with mucus hyper secretion but no airflow obstruction (FEV1/VC <70% predicted, and in this study FEV1 <50% predicted). Age range un specified.
Results	**PaO2 & FEV1** - No significant differences occurred between the controls and pts receiving physiotherapy and IPPV. **Sputum volumes** – The only significant difference found was in those patients receiving physiotherapy in group 1 who produced more sputum in the last three days in hospital than their respective controls ($p<0.05$). **Morbidity in hospital** – No significant differences **Mortality in hospital** – No significant differences **Duration of hospital stay** – No significant differences
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b
NCC CC ID	1341

Author / Title / Reference / Yr	Brown, P. A., Manfreda, J., McCarthy, D. S., MacDonald, S. (1987). The effect of mechanical vibration in patients with acute exacerbations of chronic obstructive pulmonary disease. Physiotherapy Canada, 39, 6, 371-374.
N=	N= 24 participants Location= Physiotherapy at the Respiratory Hospital, Health Sciences Centre, Canada Sites=1
Research Design	RCT randomised cross-over trial.
Aim	To assess the efficacy of mechanical vibration in patients with acute exacerbations of chronic obstructive pulmonary disease.
Operational Definition	In and out patients with • a chronic productive cough with sputum expectoration of 30 ml or greater in 24 hours. • an acute episode of pneumonia determined by chest x-ray, or exacerbation of COPD with an increased sputum expectoration of 30ml or greater in 24 hours. An exacerbation was defined according to Stenhouse as an increase in the quantity or purulence of sputum.
Population	Patients with acute exacerbations of chronic obstructive pulmonary disease.
Intervention	Vibration N=24 Intervention: All patients were in a sitting position, leaning forward with elbows supported on a table and head resting on a pillow. Vibration was administered to the chest wall over laying the affected segment for 15 minutes using the Wahl vibrator (model 4300). The vibrator was applied with firm pressure and moved to adjacent areas at approximately 30-second intervals thereby covering the required surface area. If more than one segment was involved, the time was increased accordingly. Patients were not given specific instructions regarding breathing exercises or coughing frequency. They were instructed to expectorate sputum following spontaneous coughing.
Comparison	Positioning alone N=24 Cross-over occurred for positioning alone 24 hours later.
Outcome	• FEV1 • FVC • SaO_2 • FEV1, FVC and oxygen saturation were recorded at 5 minutes, 30 minutes, and 1 and 24 hours post procedure. Sputum was collected in measured containers and the volume was recorded at 60 minutes post procedure and 24 hours following the procedure.
Characteristics	• Males/females= 71%/29% • Mean age= 66.5yrs • FEV1 % predicted= 33.4 • FVC % predicted= 57.4

	• FEV1/FVC= 49.1 • Usual 24hrs sputum (ml)= 65
Results	**FEV1 and FVC** No significant difference was found in the FEV1 and FVC, at any one of the time intervals recorded, after patients had received the vibration and on the control day when they maintained positioning without any intervention. **Sputum volume** At the 60 minute time interval, significantly more volume of sputum was recorded following vibration than on the control day when they received positioning alone ($p<0.05$). Sputum volumes expectorated within 24 hours were not significantly different between treatment and control days. **SaO_2** The oxygen saturation values for all subjects are not significantly different between vibration and control days at any of the time intervals including pre-treatment measurements. However, when patients on room air were separated from those on supplemental oxygen, there was a significantly greater oxygen saturation post vibration than post positioning at 30 minutes in the group receiving supplemental oxygen ($p<0.05$). There was no difference in oxygen saturation at 60 minutes following vibration in comparison with positioning for either room air patients or patients with supplemental oxygen.
SIGN Quality Rating	+
Hierarchy of Evidence Grading	Ib
NCC CC ID	1497