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