

**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.]", <i>JAMA</i> , 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", <i>Chest</i> , 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", <i>JAMA</i> , 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", <i>Chest</i> , 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. <i>Ann Intern Med</i> , 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. <i>Eur Respir J</i> , 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.]", <i>JAMA</i> , 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

<i>Duration, Mean (SD)</i>	<i>Overall</i>	<i>COPD</i>	<i>ARDS</i>	<i>p value</i>
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
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Author / Title / Reference / Yr	Nevins, M. L. & Epstein, S. K. 2001, "Predictors of outcome for patients with COPD requiring invasive mechanical ventilation", <i>Chest</i> , 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).

	<p>COPD exacerbation (without co-morbid illness)=12% COPD exacerbation=15%</p> <p>There were no significant differences between the survivors and non survivors regarding outpatient therapy (theophylline, inhaled or oral steroids, home O2) or smoking status.</p> <p>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)</p> <p>Poor outcome predictors associated with a higher in hospital mortality</p> <ul style="list-style-type: none"> • 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% CI 1.07 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 <p>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”.</p>
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" <i>JAMA</i> vol
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	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	<p>% 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.</p> <p>(Other data presented in paper, as per below, is <u>not</u> ventilator / non ventilator stratified)</p> <p>Mortality 24% at hospital discharge 9% ICU mortality</p> <p>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%</p> <p>Mortality aged >65yrs 216/362 (60%) were aged > 65yrs and survival status up to 1 yr after hospital discharge was available for 167 pts.</p>

	<p>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</p> <p>Hospital mortality and important predictors in pts N=167 aged>65yrs (Multiple regression analysis) p<0.05</p> <ul style="list-style-type: none"> • 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", <i>Chest</i> , 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	<ul style="list-style-type: none"> • 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	<p>Mortality rate Pts with FEV1 <1L - 44% mortality rate Pts with FEV1 >1L - 42% mortality rate</p> <p>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%.</p> <p>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.</p> <p>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.</p> <p>FEV1 MRR 95% CI 0.40 147 16 to 1380</p>

	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	<ul style="list-style-type: none"> • Arterial blood gases • Duration of mechanical ventilation • Time in the intensive care unit • Occurrence of nosocomial pneumonia • Survival at 60 days
Characteristics	<ul style="list-style-type: none"> • 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 ratio= 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). <ul style="list-style-type: none"> • <u>Arterial blood gases</u>

	<p>Invasive ventilation significantly improved blood gas values ($p < 0.001$) in the two groups of patients at admission.</p> <ul style="list-style-type: none"> • <u>Duration of mechanical ventilation</u> 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; $p = 0.021$). • <u>Time in the intensive care unit</u> 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; $p = 0.005$). • <u>Occurrence of nosocomial pneumonia</u> 28% of patients in the invasive ventilation group and no patients in the non-invasive ventilation group developed nosocomial pneumonia. • <u>Survival at 60 days</u> Mortality rate at 60 days was significantly higher in the invasive ventilation group compared to the non- invasive ventilation group (92% and 72%; $p = 0.009$). • <u>Lung function at discharge</u> 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	<p>Outcomes assessed:</p> <ul style="list-style-type: none"> • Predictive factors for the weaning process. • Survival of the COPD patients • Predictive factors for survival <p>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:</p> <ul style="list-style-type: none"> • Anthropometric data • Arterial blood gases • Serological status • Nutritional status • Pulmonary function test • Number of pulmonary exacerbations
Characteristics	<p>Age Successfully/unsuccessfully weaned group= 67yrs/66yrs PaO₂ kPa Successfully/unsuccessfully weaned group= 6.8/5.8 PaCO₂ kPa Successfully/unsuccessfully weaned group= 7.0/9.1 PaO₂/FIO₂ on MV Successfully/unsuccessfully weaned group= 30.8/26.9 PaCO₂/FIO₂ 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.</p>
Results	<ul style="list-style-type: none"> • <u>Predictive factors for the weaning process</u> Only six of the variables considered (Paco₂ kPa, Pao₂ kPa, MIP cmH₂O, P₀₁ cmH₂O, 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 Paco₂ (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> <i>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</i>

	<p>40%.</p> <ul style="list-style-type: none"> • <u>Predictive factors for survival</u> <p>The authors were unable to predict the survival rate. The best equation including Paco₂, Pao₂, age and serum protein level, could correctly predict the survival at one year in only 52% of the patients.</p>
SIGN Quality Rating	-
Hierarchy of Evidence Grading	IIa
NCC CC ID	1718