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# Use of non-invasive ventilation to wean critically ill adults off invasive ventilation: meta-analysis and systematic review

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## ABSTRACT

**Objective** To summarise the evidence for early extubation with immediate application of non-invasive ventilation compared with continued invasive weaning on important outcomes in intubated adults with respiratory failure.

**Design** Systematic review and meta-analysis of randomised and quasi-randomised controlled trials.

**Setting** Intensive care units.

**Participants** Critically ill adults receiving invasive ventilation.

**Study selection criteria** We searched Medline, Embase, and CENTRAL, proceedings from four conferences, and reference lists of relevant studies to identify relevant trials. Two reviewers independently selected trials, assessed trial quality, and abstracted data.

**Results** We identified 12 trials enrolling 530 participants, mostly with chronic obstructive pulmonary disease. Compared with invasive weaning, non-invasive weaning was significantly associated with reduced mortality (relative risk 0.55, 95% confidence interval 0.38 to 0.79), ventilator associated pneumonia (0.29, 95% 0.19 to 0.45), length of stay in intensive care unit (weighted mean difference −6.27 days, −8.77 to −3.78) and hospital (−7. 19 days, −10.80 to −3.58), total duration of ventilation, and duration of invasive ventilation. Non-invasive weaning had no effect on weaning failures or weaning time. Benefits on mortality and weaning failures were non-significantly greater in trials that exclusively enrolled patients with chronic obstructive pulmonary disease versus mixed populations.

**Conclusions** Current trials in critically ill adults show a consistent positive effect of non-invasive weaning on mortality and ventilator associated pneumonia, though the net clinical benefits remain to be fully elucidated. Non-invasive ventilation should preferentially be used in patients with chronic obstructive pulmonary disease in a highly monitored environment.

## INTRODUCTION

Patients with respiratory failure often require mechanical ventilation to unload the respiratory muscles and support gas exchange until the pathophysiology leading to respiratory failure improves. Invasive ventilation maintains a patent airway but when used over a prolonged period of time might lead to ventilator associated pneumonia.[1] This, in turn, is associated with increased morbidity and trends towards increased mortality.[2] For these reasons, clinicians caring for patients who need invasive ventilation strive to reduce the duration of invasive ventilation while optimising the chance for successful extubation.[3]

Non-invasive ventilation provides an alternative method of supporting a patient's respiration by using positive pressure ventilation with either an oronasal, nasal, or total face mask at the patient-ventilator interface. Non-invasive ventilation preserves the patient's ability to speak and cough[4] and has been shown to reduce complications related to intubation, especially ventilator associated pneumonia.[5,6] Similar to invasive ventilation, non-invasive ventilation can reduce the frequency of breathing, augment tidal volume, improve gas exchange, and rest the muscles of respiration.[7,8] Non-invasive ventilation has been widely investigated as an initial treatment to prevent intubation and intubation related complications and improve clinical outcomes in selected patients.[9,10] Many patients with severe respiratory failure, impaired sensorium, haemodynamic instability, or difficulty clearing secretions, however, undergo direct intubation or intubation after a failed attempt at non-invasive ventilation.

To mitigate the effect of complications associated with protracted invasive ventilation, investigators have explored the role of non-invasive ventilation in weaning patients from invasive ventilation. Non-invasive weaning involves extubating patients directly to non-invasive ventilation for the purpose of weaning to reduce the duration of invasive ventilation and, consequently, complications related to intubation. Since Udwadia and colleagues published the first report describing use of non-invasive ventilation to facilitate liberation of patients with weaning failure from invasive ventilation in 1992,[11] several uncontrolled, prospective studies,[12-15] early randomised controlled trials,[w1-w5] and an early meta-analysis[16] have examined its use to facilitate weaning. That meta-analysis showed significant benefit of the non-invasive approach on length of stay in hospital and the total duration of ventilation. Non-invasive weaning also reduced mortality

and ventilator associated pneumonia compared with invasive weaning, however there were few events.

In light of new evidence we critically appraised, summarised, and updated current work on the effect of non-invasive weaning compared with invasive weaning on the primary outcome of mortality and secondary outcomes including ventilator associated pneumonia, length of stay in intensive care and in hospital, and duration of ventilator support in critically ill mechanically ventilated adults.

## METHODS

### Data sources and searches

We updated a previously conducted search of Medline (January 1966-April 2008), Embase (January 1980-April 2008), and the Cochrane Central Register of Controlled Trials (Cochrane Library, Issue 2, 2008) without language restrictions. Details of the search strategy and terms are available from the authors. Two reviewers (KEAB, NKJA) screened citation titles and abstracts independently. All potentially eligible studies were retrieved in full and translated into English, as required. One reviewer (SPK) updated manual searches of abstracts from intensive care conference proceedings published in the *American Journal of Respiratory and Critical Care Medicine*, *Intensive Care Medicine*, *Critical Care Medicine*, and *Chest* from January 2003 to April 2008. We reviewed bibliographies of all retrieved articles to identify potentially relevant trials and contacted authors of included studies to identify unpublished studies and obtain additional information regarding study methods, where needed.

### Study selection

We included randomised trials that enrolled adults with respiratory failure who required invasive mechanical ventilation for at least 24 hours. The trials examined extubation with immediate application of non-invasive ventilation compared with continued invasive weaning. We included trials reporting at least one of mortality (primary outcome), ventilator associated pneumonia, weaning failure (using authors' definitions), length of stay in intensive care or hospital, total duration of ventilation (invasive and non-invasive), duration of ventilation related to weaning (after randomisation), duration of invasive ventilation, adverse events, or quality of life. We also included quasi-randomised controlled trials—for example, those that allocated patients by hospital registry number or day of the week. We excluded studies that compared non-invasive with invasive weaning in the immediate postoperative setting, compared non-invasive ventilation with unassisted oxygen supplementation, and investigated use of non-invasive ventilation after unplanned extubation. Two authors (KEAB, NKJA) independently selected articles meeting the inclusion criteria.

### Data extraction and quality assessment

Two authors (KEAB, NKJA), not blinded to the source of the reports, used a standardised data abstraction form to independently abstract data regarding study methods (randomisation, allocation concealment, cointerventions, blinded outcome assessment, completeness of follow-up, and adherence to the intention to treat principle). Additionally, we assessed features unique to the design and implementation of weaning trials, including use of daily screening to identify weaning candidates, criteria to identify weaning readiness, explicit weaning protocols (both groups), criteria for discontinuing mechanical ventilation (both groups), and reintubation. Disagreements regarding study selection and data abstraction were resolved by consensus and arbitration with a third author (SPK or MM).

### Data synthesis and statistical analysis

When there were no compelling differences in study populations, interventions, and outcomes we pooled data across studies using random effects models.[17] We derived summary estimates of relative risk and weighted mean difference with 95% confidence intervals for binary and continuous outcomes, respectively, using Review Manager 4.2.10 software (Cochrane Collaboration, Oxford). If an outcome was reported at two different time points, we included the more protracted measure in pooled analyses.

We determined the presence and impact of statistical heterogeneity among studies using the Cochran Q statistic[18] (threshold $P<0.10$)[19] and the $I^2$ test[20 21] (with threshold values of 0-40%, 30-60%, 50-90%, and ≥75% representing heterogeneity that might not be important or might represent moderate, substantial, or considerable heterogeneity, respectively).[22] In sensitivity analyses, we assessed the impact of excluding quasi-

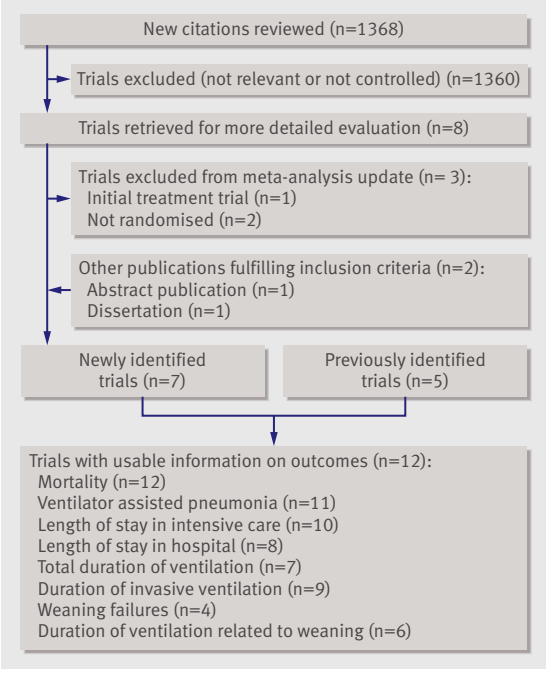


**Fig 1 | Trial selection process**

randomised trials on mortality and ventilator associated pneumonia. We planned subgroup analyses to compare the effects of non-invasive weaning on mortality and weaning failures in exclusively chronic obstructive pulmonary disease compared with non-chronic populations and on mortality in studies that enrolled ≥50% versus <50% patients with COPD. We used random effects models for sensitivity and subgroup analyses and assessed for differences between subgroups in summary estimates using a z test for interaction.

We assessed for publication bias in mortality by visually inspecting the corresponding forest plot. Post hoc, we conducted additional pooled analyses of mortality at various time points to assess the robustness of the results.

## RESULTS

### Trial identification

We identified 12 randomised trials,[w1-w12] including one quasi-randomised trial,[w4] that met our inclusion criteria. Of these, five[w1-w5] were included in a previous systematic review and meta-analysis.[16] We excluded nine trials,[w13-w21] including three new trials[w19-w21] (fig 1). The seven newly identified trials included three publications in Chinese,[w7-w9] one abstract publication,[w6] two additional publications,[w10 w11] and one unpublished dissertation[w12] (all in English). Of the previously identified trials, one was published in abstract form[w3] and one trial was published in Chinese.[w4] In total, eight trials evaluated exclusively patient with chronic obstructive pulmonary disease[w1 w4 w6-w10 w12] and four included mixed patients.[w2 w3 w5 w11] Patients were considered difficult to wean in one study[w2] and as persistent weaning failures in another study.[w5] Four studies[w7-w10] evaluated patients with chronic obstructive pulmonary disease with pulmonary infection (table 1). The two reviewers (KEAB, NKJA) achieved complete agreement on study selection.

### Initial management

Initial pre-randomisation ventilation strategies predominantly entailed volume-cycled ventilation[w1 w2 w4 w5 w6 w7 w9 w10 w12] with or without the concurrent or subsequent use of pressure support. In three trials, screening for weaning eligibility occurred daily[w3 w5 w6] or daily after 48 hours of invasive ventilation.[w2] Alternatively, candidates for weaning were identified after at least 24 hours,[w12] 36-48 hours (including 6-8 hours of paralysis),[w1] 48 hours,[w2] 48-60 hours,[w4] 72 hours (including 6-8 hours of paralysis),[w6] or three days[w5] of invasive ventilation. Eligibility for study inclusion was based on meeting predefined criteria for readiness for weaning[w1 w2 w4-w12] and failure of either a single 30 minute,[w3 w11] one hour,[w1] or two hour[w2 w6 w12] T-piece trial, or failure of two hour T-piece trials on three consecutive days.[w5]

Four studies,[w7-w10] evaluating patients with chronic obstructive pulmonary disease with pulmonary infection, enrolled patients after control of infection was achieved[w7] or when they met pulmonary infection control criteria.[w8-w10] In most trials these criteria included an improving radiograph, improvement in temperature,

**Table 1 | Populations and interventions in studies of non-invasive ventilation in critically ill adults**

| Study | No of patients | Inclusion criteria (patients) | Inclusion criteria (weaning eligibility) | Experimental strategy | Control strategy |
|---|---|---|---|---|---|
| Nava,[w1] 1998 | 50 | Exacerbation of COPD. Intubated for at least 36-48 hrs | Simple weaning criteria, 1 hr SBT failure | Non-invasive pressure support on conventional ventilator delivered with face mask | Invasive PS |
| Girault,[w2] 1999 | 33 | Acute-on-chronic respiratory failure (COPD, restrictive, or mixed populations). Intubated for at least 48 hrs | Simple weaning criteria, 2 hr SBT failure | Flow or pressure mode with nasal or face mask | Flow or pressure mode (PS) |
| Hill,[w3] 2000 | 21 | Acute respiratory failure | 30 minute SBT failure | NIV using VPAP in ST-A mode | Invasive PS |
| Chen,[w4] 2001 | 24 | Exacerbation of COPD. Intubated for at least 48-60 hrs. Saturations >88% on $FiO_2$ 40% | Day 3 + weaning criteria | Bilevel NIV (pressure mode) | Invasive PS |
| Ferrer,[w5] 2003 | 43 | Acute respiratory failure and persistent weaning failure. Intubated for at least 72 hrs | 2 hr SBT failure on 3 consecutive days | Bilevel NIV in ST mode delivered with face or nasal mask | AC or invasive PS |
| Rabie,[w6] 2004 | 37 | Exacerbation of COPD | 2 hr SBT failure | NIV (proportional assist in timed mode) delivered by face or nasal mask | Invasive PS |
| Wang,[w7] 2004 | 28 | COPD. Bronchopulmonary infection | PIC window | NIV (pressure mode) delivered by mask (unspecified) | SIMV+PS |
| Zheng,[w8] 2005 | 33 | COPD. Severe pulmonary infection | PIC window | Bilevel NIV (pressure mode) delivered by face or nasal mask | Invasive PS |
| Zou,[w9] 2006 | 76 | COPD with severe respiratory failure. Pulmonary infection | PIC window | Bilevel NIV (pressure, ST mode) delivered by nasal or oronasal mask | SIMV +PS |
| Wang,[w10] 2005 | 90 | COPD with severe hypercapnic respiratory failure. Pneumonia or purulent bronchitis. Age ≤85. Capable of self care in past year | PIC window | Bilevel NIV (pressure mode) | SIMV+PS |
| Trevisan,[w11] 2008 | 65 | Invasively ventilated >48 hours | 30 min SBT failure | Bilevel NIV (pressure mode) delivered by facemask | Invasive mechanical ventilation |
| Shiva Prasad[w12] | 30 | COPD. Hypercapnic respiratory failure | 2 hr SBT failure | Bilevel NIV (pressure mode) delivered by full face mask | Invasive PS |

COPD=chronic obstructive pulmonary disease; SBT=spontaneous breathing trial; PS=pressure support; NIV=non-invasive ventilation; PIC=pulmonary infection control; AC=assist control; SIMV=synchronised intermittent mechanical ventilation; VPAP=ventilator positive airway pressure.

**Table 2** | Quality assessment in studies of non-invasive ventilation in critically ill adults

| Study | Random assignment | Allocation concealed | Daily screening | Weaning readiness criteria | Weaning guidelines (both groups) | Discontinuation criteria (both groups) | Reintubation criteria | Control of cointerventions | Blinded outcomes assessment | Follow-up | ITT |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Nava,[w1] 1998 | Yes | Yes | No | Yes | Yes | Yes | Yes | No | No | Yes | Yes |
| Girault,[w2] 1999 | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes |
| Hill,[w3]* 2000 | Yes | Yes | Yes | Uncertain | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Chen,[w4] 2001 | Quasi | No | No | Yes | No | Yes | No | Yes | No | Yes | Yes |
| Ferrer,[w5] 2003 | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No | Yes | Yes |
| Rabie,[w6] 2004 | Yes | Yes | No | Yes | Yes | Yes | Yes | No | No | Yes | Yes |
| Wang,[w7] 2004 | Yes | Uncertain | No† | Yes | No | Yes | No | Yes | No | Yes | Yes |
| Zheng,[w8] 2005 | Yes | Uncertain | No‡ | Yes | Yes | Yes | No | Yes | No | Yes | Yes |
| Zou,[w9] 2006 | Yes | Uncertain | No‡ | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes |
| Wang,[w10] 2005 | Yes | Uncertain | No‡ | Yes | No | Yes | Yes | Yes | No | Yes | Yes |
| Trevisan,[w11] 2008 | Yes | Yes | No | Yes | No | No | No | No | No | Yes | Yes |
| Shiva Prasad[w12] | Yes | Uncertain | No | Yes | Yes | Yes | No | Yes | No | Yes | Yes |

Quasi=quasi-randomised; ITT=intention to treat.
*Abstract.
†Infection under control.
‡ Pulmonary infection control criteria.

improvement in white blood cell count (or percentage of neutrophils), and reduced volume and tenacity of secretions,[w7-w10] with improved haemodynamics, cough, and level of consciousness[w7 w9] or reduced ventilator settings.[w10]

### Invasive weaning

Patients in the control groups were variably weaned with pressure support,[w1-w6 w8 w12] assist control,[w5] or synchronised intermittent mandatory ventilation with pressure support.[w7 w9 w10] The level of support was gradually decreased in two studies[w1 w5] and trials of spontaneous breathing, using T-piece or continuous positive airway pressure of less than 5 cm $H_2O$, were performed twice daily[w1] or daily[w5 w11] until extubation. One study included at least two observation periods per day during pressure support weaning with optional trials of spontaneous breathing.[w2] One study each titrated pressure support either by 2 cm $H_2O$ every four hours according to clinical tolerance, saturations, and respiratory rate[w12] or by 2-4 cm $H_2O$ per day.[w6] Patients were considered weaned when they remained stable for at least four hours with a synchronised intermittent mandatory ventilation rate of 5 breaths/minute with pressure support of 5-7 cm $H_2O$[w10]; blood gases were normalised, and patients could breathe spontaneously for more than three hours with low oxygen requirements (fractional concentration of inspired oxygen ($FiO_2$) ≤0.40), acceptable saturations (pulse oximetry saturation ($SpO_2$) ≥90%), and a normal pH (pH ≥7.35)[w7]; or when pressure support was titrated to ≤8 cm $H_2O$ [w8] or ≤10 cm $H_2O$[w9 w12] with positive end expiratory pressure of 5 cm $H_2O$,[w12] and satisfactory blood gases,[w12] saturations,[w8 w9] respiratory rate,[w8 w9 w12] tidal volume (about 8 ml/kg body weight),[w8 w9] and partial pressure of carbon dioxide ($PaCO_2$, between 45 and 60 mm Hg or at baseline levels) on low $FiO_2$[w8 w9 w12] for more than four hours.[w8 w9] To discontinue invasive ventilation, patients successfully completed a spontaneous breathing trial of either two hours,[w3 w5] three hours,[w1 w4 w7] or unspecified duration,[w11] or two periods of observation with optional spontaneous breathing trials.[w2]

### Non-invasive weaning

Similar to invasive weaning, trials applied different protocols for non-invasive weaning. After extubation, in 11 studies non-invasive ventilation was administered in pressure mode,[w1-w5 w7-w12] of which five specified a spontaneous timed mode[w2 w3 w5 w9 w12] or flow mode.[w2] Another study used proportional assist ventilation in timed mode.[w6] Non-invasive ventilation was delivered by face mask[w1-w3 w5 w6 w8-w12] or nasal mask.[w2 w3 w5 w6 w8 w9] Initial support was delivered continuously in five studies,[w1 w3-w5 w12] intermittently in one study,[w2] for at least two hours during the initial application in one study,[w9] or until tolerated for 20-22 hours a day (spaced by periods of spontaneous ventilation during meals and for expectoration) in one study.[w6] The level of support was gradually decreased and the duration on non-invasive ventilation gradually reduced.[w8 w9] Some trials permitted fixed or gradually increasing periods of spontaneous breathing,[w1 w6] with at least two[w1 w6] specifying two periods of spontaneous breathing a day. In some studies, clinicians titrated pressure support by 2 cm $H_2O$ every four hours[w12] or by 2-4 cm $H_2O$ each day[w6] according to the patient's tolerance. In some studies, clinicians decreased the level of inspiratory and expiratory positive airway pressure to 8 cm and 4 cm $H_2O$, respectively,[w12] while in others, inspiratory pressure was reduced to <10 cm $H_2O$ (with non-invasive ventilation applied for less than two hours a day),[w8 w9] or until the difference between inspiratory and expiratory pressure (the equivalent of pressure support) was <5 cm $H_2O$.[w10] Criteria for discontinuing non-invasive support included successful completion of a three[w1 w4] or two[w3] hour period of spontaneous

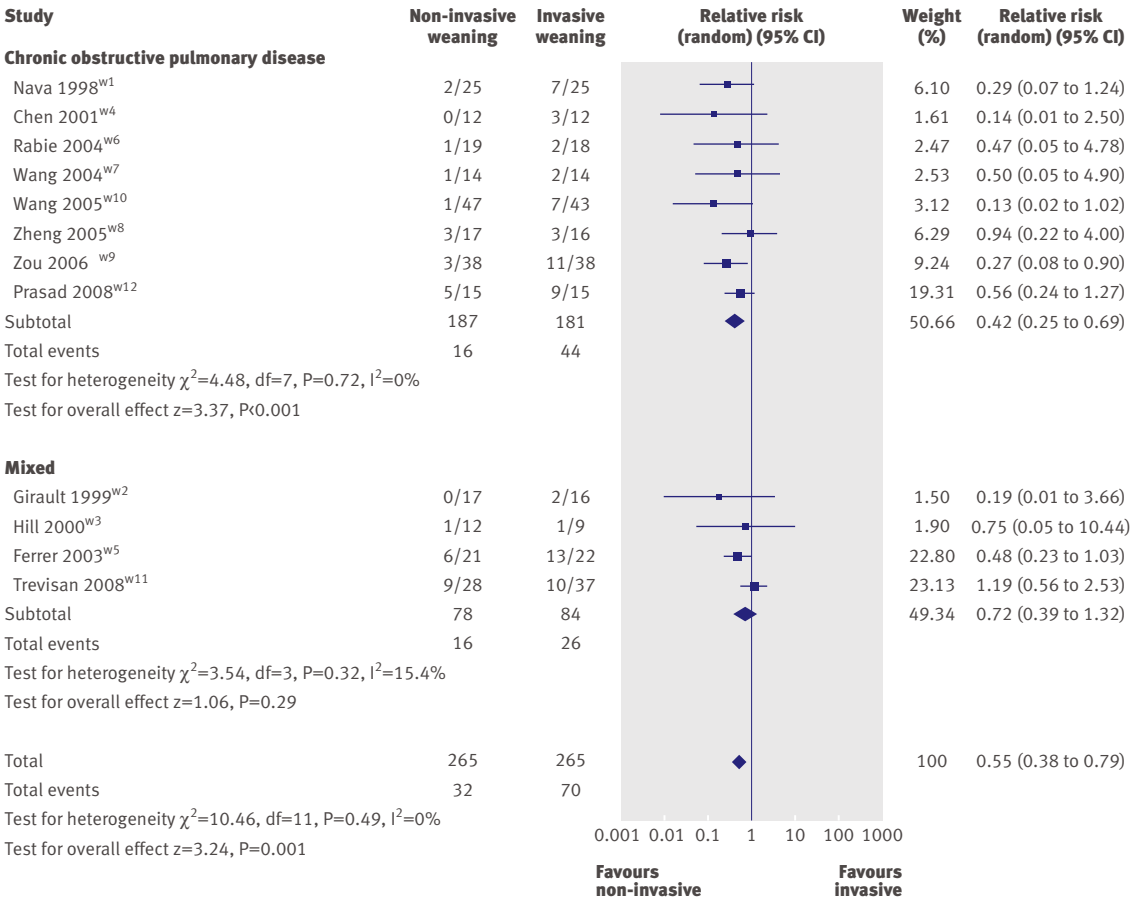


**Fig 2** | Effect of non-invasive and invasive weaning on mortality in critically ill adults on invasive ventilation

breathing or at least two periods of spontaneous breathing observed by an attending physician.[w2]

### Quality assessment

We contacted authors to confirm and supplement information related to study methods where needed; nine study authors responded.[w1-w3 w5 w6 w9 w11 w12] Overall, the included studies were of moderate to high quality (table 2).

### Primary outcome: mortality

All 12 trials (530 patients) provided mortality data, reported at 30 days,[w12] 60 days,[w1] 90 days,[w2 w5] at hospital discharge,[w6 w9-w11] or at an undefined time.[w3 w4 w7] There was strong evidence that non-invasive weaning was associated with reduced mortality (relative risk 0.55, 95% confidence interval 0.38 to 0.79, P=0.001), with no heterogeneity (table 3, fig 2).

### Secondary outcomes

Pooled data from 11 studies (509 patients)[w1 w2 w4-w12] showed that non-invasive weaning was associated with decreased ventilator associated pneumonia (relative risk 0.29, 0.19 to 0.45, P<0.001), with no heterogeneity (fig 3). Nine studies provided diagnostic criteria for ventilator associated pneumonia.[w1 w4 w5 w7-w12] Meta-analyses also showed that patients undergoing non-invasive weaning had clinically and statistically reduced length of stay in intensive care (6.3 days) and hospital (7.2 days), total duration of mechanical ventilation (5.6 days), and duration of invasive ventilation (7.8 days), with significant heterogeneity. Non-invasive weaning had no effect on the duration of mechanical ventilation related to weaning or weaning failures, and no study reported on quality of life.

### Adverse events

Notwithstanding few events and wide confidence intervals, the pooled results showed no difference in arrhythmias (two studies, 63 patients) or reintubation (six studies, 328 patients), and significantly fewer tracheostomies (three studies, 141 patients) with non-invasive weaning (table 3).

### Sensitivity and subgroup analyses

Exclusion of a quasi-randomised trial[w4] maintained the significant reductions in mortality (relative risk 0.56, 0.39 to 0.81, P=0.002) and ventilator associated pneumonia (0.30, 0.20 to 0.47, P<0.001) in favour of non-invasive weaning. We noted a non-significant beneficial effect (z=−1.332; P=0.18) of non-invasive weaning in patients with chronic obstructive pulmonary disease (eight studies) compared with mixed populations (four studies) (0.42, 0.25 to 0.69, and 0.72, 0.39 to 1.32). When we conducted a subgroup analysis evaluating

studies enrolling ≥50% (10 studies) versus <50% (two studies) patients with chronic obstructive pulmonary disease, we found a significant benefit of non-invasive weaning on mortality in favour of studies enrolling predominantly patients with chronic obstructive pulmonary disease (0.43, 0.28 to 0.65, and 1.15, 0.56 to 2.37; z=−2.308; P=0.02). Similarly, we noted a non-significant but greater effect of non-invasive weaning on weaning failures in patients with chronic obstructive pulmonary disease (two studies) compared with mixed populations (two studies) (0.50, 0.22 to 1.12, and 1.28, 0.45 to 3.60, (z=−1.395; P=0.16).

### Publication bias

Visual inspection of a funnel plot comparing the study estimates of effect (relative risk) with the standard error of the log relative risk of mortality showed asymmetry and suggested the absence of studies with non-significant results. The absence of such trials might overinflate the overall summary estimate of effect.[22]

## DISCUSSION

In critically ills adults in intensive care non-invasive weaning is associated with decreased mortality, ventilator associated pneumonia, length of stay in intensive care and hospital, total duration of mechanical ventilation, and duration of invasive ventilation. None of the 12 trials in our review reported quality of life outcomes.

In their efforts to optimise the timing of liberation from invasive ventilation, clinicians are challenged by a trade-off between the risks associated with failed extubation and the complications associated with prolonged invasive ventilation.[23] Non-invasive weaning, by providing ventilatory support without an artificial airway, offers a potential solution to this trade-off. Clinicians might be reluctant to adopt the non-invasive approach to weaning, however, because of the need to surrender a protected airway, concerns regarding the ventilatory support that can be provided with non-invasive ventilation, and the increased risk of ventilator associated pneumonia if reintubation is required.[24] Moreover, the optimal timing for transitioning patients to non-invasive ventilation for weaning remains to be determined.

Most studies in our review included patients with predominantly[w2 w5] or exclusively[w1 w4 w6-w10 w12] chronic obstructive pulmonary disease. Patients with chronic obstructive pulmonary disease might be ideally suited to non-invasive ventilation given its ability to offset respiratory muscle fatigue and tachypnoea, augment tidal volume, and reduce intrinsic positive end expiratory pressure.[9 25] Subgroup analyses suggested greater benefits of non-invasive weaning in patients with chronic obstructive pulmonary disease, although results of analyses of subgroup effects were predominantly non-significant. Inferences from the subgroup analyses are limited by contamination of mixed populations with patients with chronic obstructive pulmonary disease, the small number of studies evaluating non-invasive weaning in patients with other causes of respiratory failure, and are probably underpowered to detect significant interactions. Whether other causes of respiratory failure are as amenable to non-invasive weaning remains to be determined.

We found that non-invasive weaning significantly reduced mortality and length of stay in intensive care and hospital consistent with (and possibly due to) the observed reduction in ventilator associated pneumonia. Direct access to respiratory secretions among invasively weaned patients, however, might have enhanced detection of ventilator associated pneumonia in this group. Moreover, in the control groups mortality (range 11.1%[w3 w6] to 60.0%[w12]) and rates of ventilator associated pneumonia (range 6.3%[w2] to 59.1%[w5]) varied among the included trials. The small number of events in the included studies,[26] the variability in event rates in control groups, and the absence of a

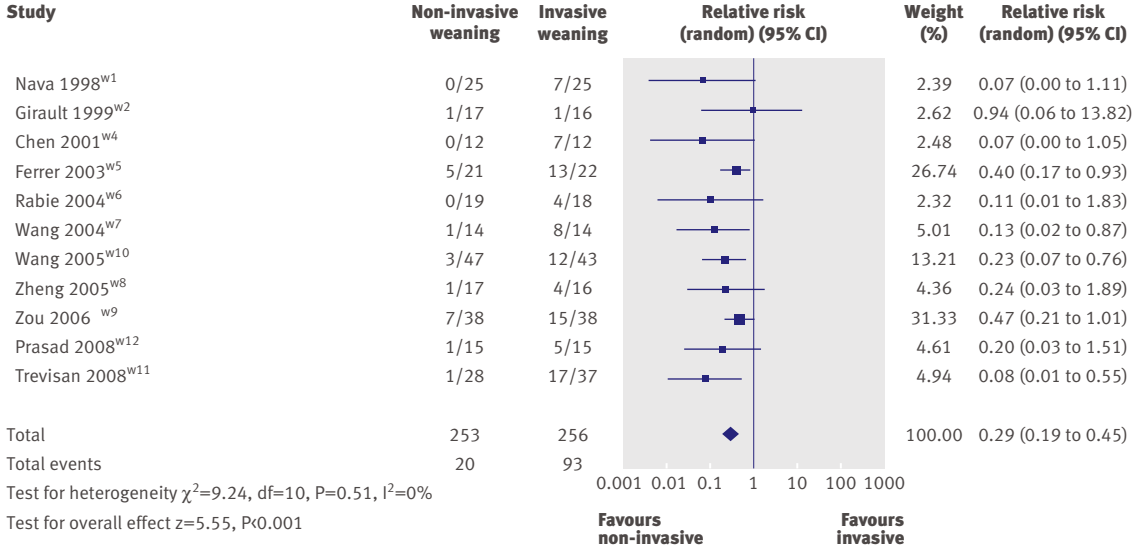


**Fig 3** | Effect of alternative weaning strategies on ventilator associated pneumonia in critically ill adults on invasive ventilation

**Table 3** | Summary estimates of effect of non-invasive ventilation in critically ill adults

| Outcome | No studies (No of patients) | Summary estimate (95% CI) | P value (summary estimate) | P value (heterogeneity) | $I^2$ (%) |
|---|---|---|---|---|---|
| Mortality | 12 (530) | 0.55* (0.38 to 0.79) | 0.001 | 0.49 | 0 |
| VAP | 11 (509) | 0.29* (0.19 to 0.45) | <0.001 | 0.51 | 0 |
| Weaning failures | 4 (141) | 0.72* (0.37 to 1.42) | 0.34 | 0.35 | 9.2 |
| Length of stay: | | | | | |
| Intensive care | 10 (485) | −6.27† (−8.77 to −3.78) | <0.001 | <0.001 | 77.4 |
| Hospital | 8 (401) | −7.19† (−10.80 to −3.58) | <0.001 | <0.001 | 76.8 |
| Duration of mechanical ventilation: | | | | | |
| Total | 7 (385) | −5.64† (−9.50 to −1.77) | 0.004 | <0.001 | 85.6 |
| Related to weaning | 6 (224) | −0.94† (−3.24 to 1.36) | 0.42 | <0.001 | 91.8 |
| Endotracheal‡ | 9 (391) | −7.81† (−11.31 to −4.31) | <0.001 | <0.001 | 89.9 |
| Adverse events: | | | | | |
| Reintubation | 6 (328) | 0.73* (0.40 to 1.34) | 0.31 | 0.19 | 32.4 |
| Tracheostomy | 3 (141) | 0.16* (0.04 to 0.75) | 0.02 | 0.30 | 17.2 |
| Arrhythmia | 2 (63) | 1.05* (0.17 to 6.67) | 0.96 | 0.35 | 0 |

VAP=ventilator associated pneumonia.
*Relative risk.
†Weighted mean difference.
‡Invasive ventilation.

single adequately powered randomised controlled trial directly comparing the alternative weaning strategies limits the strength of our inferences.

While surviving admission to hospital is undoubtedly an important outcome for patients and healthcare providers, it can be influenced by many factors resulting in highly variable lengths of stay. Patients might remain in hospital at arbitrary time points (such as 60 days) because of factors related and unrelated to the initial illness that precipitated admission. This might not only influence the distribution of events between two treatment arms but might also underestimate mortality (biasing towards a mortality benefit). Conversely, extended follow-up might be influenced by additional deaths unrelated to the treatment of interest (biasing against a mortality benefit). To examine the potential influence of measuring mortality at various time points, we pooled study estimates of mortality using random effects models in three categories: mortality or time in intensive care not specified (six trials) (relative risk 0.63, 0.32 to 1.25, P=0.18); hospital, inpatient, or 30 day mortality (seven trials) (0.56, 0.31 to 1.01, P=0.05); and 60-90 day mortality (three trials) (0.42, 0.21 to 0.80, P=0.009). While underpowered to detect differences (with fewer events and trials at each time point), the pooled results support a qualitatively similar direction of treatment effect in favour of non-invasive weaning.

The included studies varied in the methods used to identify candidates for weaning and to titrate and discontinue mechanical support. Multidisciplinary protocols to identify candidates for weaning and for the conduct of daily trials of spontaneous breathing reduce the duration of mechanical ventilation.[27-33] In our meta-analysis, while only three trials screened daily for readiness for trials of spontaneous breathing, four additional trials conducted pre-randomisation trials of spontaneous breathing, and four trials assessed for resolution of pulmonary infection to identify weaning readiness. The latter strategy prioritises resolution of the cause of respiratory failure (bronchopulmonary infection) over meeting conventional weaning criteria and represents a novel approach to identifying candidates for weaning in selected populations. In trials that did not include a trial of spontaneous breathing after randomisation, however, some invasively ventilated patients might have been ventilated longer than necessary. While methods for identifying candidates for weaning might affect study estimates of the duration of ventilation, they represent pre-randomisation study design considerations and are less likely to result in important performance bias. Conversely, unequal or inconsistent use of weaning protocols and the frequency with which periods of spontaneous breathing (non-invasive strategy) or trials of spontaneous breathing (invasive strategy) were permitted represent important post-randomisation study design considerations that could bias estimates of the duration of ventilation in unblinded weaning trials. Opportunities for comparable reductions in mechanical support were provided by using weaning protocols or guidelines in both treatment groups in seven trials with variable use of periods of spontaneous breathing (or trials of spontaneous breathing) among the included studies. Whereas 11 trials reported use of criteria to discontinue mechanical ventilation in both groups, only six reported explicit reintubation criteria after a failed attempt at extubation. While recent literature supports that administration of sedation is an important consideration in study design, with the potential to affect length of ventilation,[34] only one study in our review used a sedation protocol.[w3] Overall, most trials included measures to reduce bias after randomisation and were of moderate to high quality, though variation among trials in adopting these measures limits interpretation of some of the pooled results.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Non-invasive ventilation has been widely investigated as an initial treatment to prevent intubation and intubation related complications

Many patients with severe respiratory failure, impaired sensorium, haemodynamic instability, or difficulty clearing secretions undergo direct intubation or intubation after a failed attempt at non-invasive ventilation

## WHAT THIS STUDY ADDS

Non-invasive weaning was associated with decreased mortality, ventilator associated pneumonia, length of stay in intensive care and hospital, total duration of mechanical ventilation, and duration of invasive ventilation

This review was strengthened by an extensive search for relevant trials. We conducted duplicate independent citation screening and data abstraction and corresponded with lead investigators to clarify study methods where needed. In addition to appraising the quality of randomised trials, we also assessed methodological features specific to weaning trials that might influence estimates of treatment effect. We used random effects models in pooling data, which take into consideration variation both between and within studies. Pooling results in a meta-analysis implicitly assumes that the studies are sufficiently similar with respect to their populations, study interventions, outcomes, and methodological quality that one could reasonably expect a comparable underlying treatment effect. A priori, we planned sensitivity and subgroup analyses to explain the differences among study results and anticipating heterogeneity in pooling across studies for selected outcomes.

### Conclusion

Current trials of non-invasive weaning, while limited by inclusion of small numbers of patients mostly with chronic obstructive pulmonary disease, consistently show positive effects on mortality and ventilator associated pneumonia. The evidence of benefit is promising, but additional trials are required to fully evaluate the net clinical benefits on clinical outcomes associated with non-invasive weaning, especially the risks associated with extubation and the impact of reintubation after a failed attempt at extubation on clinical outcomes. If consideration is being given to weaning patients with non-invasive ventilation, we suggest that it be preferentially used in patients with chronic obstructive pulmonary disease and applied in a highly monitored environment. A well designed, adequately powered randomised controlled with explicitly defined end points comparing the alternative approaches to weaning is justified.

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1 Pingleton SK. Complications of acute respiratory failure. *Am Rev Respir Dis* 1988;137:1463-9.
2 Heyland DK, Cook DJ, Griffith L, Keenan SP, Brun Buisson C. The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. Canadian Critical Care Trials Group. *Am J Respir Crit Care Med* 1999;159:1249-56.
3 MacIntyre NR, Cook DJ, Ely EW Jr, Epstein SK, Fink JB, Heffner JE, et al. Evidence based guidelines for weaning and discontinuing ventilatory support. A collective task force facilitated by the American College of Chest Physicians, the American Association for Respiratory Care and the College of Critical Care Medicine. *Chest* 2001;120(suppl 6):375-95S.
4 Mehta S, Hill NS. Noninvasive ventilation. *Am J Respir Crit Care Med* 2001;163:540-77.
5 Antonelli M, Conti G, Rocco M, Bufi M, DeBlasi RA, Vivino G, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med* 1998;339:429-35.
6 Nourdine K, Combes P, Carton MJ, Beure Cannamea A, Ducreux JC. Does noninvasive ventilation reduce the ICU nosocomial infection risk? A prospective clinical survey. *Intensive Care Med* 1999;25:567-73.
7 Nava S, Ambrosino N, Rubini F, Fracchia C, Rampulla C, Torri G, et al. Effects of nasal pressure support ventilation and external PEEP on diaphragmatic activity in patients with severe stable COPD. *Chest* 1993;103:143-50.
8 Vittaca M, Ambrosino N, Clini E, Porta R, Rampulla C, Lanini B, et al. Physiological response to pressure support ventilation delivered before and after extubation in patients not capable of totally spontaneous autonomous breathing. *Am J Respir Crit Care Med* 2001;164:638-41.
9 Keenan SP, Sinuff T, Cook DJ, Hill N. Which patient with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation? A systematic review of the literature. *Ann Intern Med* 2003;138:861-70.
10 Keenan SP, Sinuff T, Cook DJ, Hill NS. Does noninvasive positive pressure respiration improve outcome in patients with hypoxemic respiratory failure? *Crit Care Med* 2004;32:2516-23.
11 Udwadia ZF, Santis GK, Steven MH, Simonds AK. Nasal ventilation to facilitate weaning in patients with chronic respiratory insufficiency. *Thorax* 1992;47:715-8.
12 Goodenberger DM, Couser JI Jr, May JJ. Successful discontinuation of ventilation via tracheostomy by substitution of nasal positive pressure ventilation. *Chest* 1992;102:1277-9.
13 Restrick LJ, Scott AD, Ward EM, French Ro, Cornwell WE, Wedjicha JA. Nasal intermittent positive-pressure ventilation in weaning intubated patients with chronic respiratory disease from assisted intermittent positive pressure ventilation. *Respir Med* 1993;87:199-204.
14 Gregoretti C, Beltrame F, Lucangelo U, Burbi L, Conti G, Turello M, et al. Physiologic evaluation of non-invasive pressure support ventilation in trauma patients with acute respiratory failure. *Intensive Care Med* 1998;24:785-90.
15 Kilger E, Briegel J, Haller M, Frey L, Schelling G, Stoll C, et al. Effects of noninvasive positive pressure ventilatory support in non-COPD patients with acute respiratory insufficiency after extubation. *Intensive Care Med* 1999;25:1374-80.
16 Burns KEA, Adhikari NKJ, Meade MO. Noninvasive positive pressure ventilation as a weaning strategy for intubated adults with respiratory failure. *Cochrane Database Syst Rev* 2003;(4):CD004127.
17 Der Simonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
18 Cochran W. The combination of estimates from different experiments. *Biometrics* 1954;10:101-29.
19 Berlin JA, Laird NM, Sachs HS, Chalmers TC. A comparison of statistical methods for combining event rates from clinical trials. *Stat Med* 1989;8:141-51.
20 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-58.
21 Higgins JP, Thomson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta analyses. *BMJ* 2003;327:557-60.

22 Higgins JPT, Green S, eds. *Cochrane handbook of systematic reviews of interventions*. Version 5.0.1. Chichester: John Wiley, 2008.
23 Epstein SK, Ciabotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. *Chest* 1997;112:186-92.
24 Pawar M, Mehta Y, Khurana P, Chaudhary A, Kulkarni V, Trehan N. Ventilator associated pneumonia: incidence, risk factors, outcome and microbiology. *J Cardiothorac Vasc Anesth* 2003;17:22-8.
25 Nava S, Bruchi C, Rubini F, Palo A, Iotti G, Braschi A. Respiratory response and inspiratory effort during pressure support ventilation in COPD patients. *Intensive Care Med* 1995;21:871-9.
26 Devereaux PJ, Yusuf S, Yang H, Choi P, Guyatt GH. Are the recommendations to use perioperative beta-blocker therapy in patients undergoing noncardiac surgery based on reliable evidence? *CMAJ* 2004;171:245-7.
27 Ely EW, Meade MO, Haponik EF, Kollef MH, Cook DJ, Guyatt GH, et al. Mechanical ventilator weaning protocols driven by nonphysician health-care professionals: evidence-based clinical practice guidelines. *Chest* 2001;120(6 suppl):454-63S.
28 Ely EW, Baker AM, Dunagan DP, Burke HL, Smith AC, Kelly PT, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med* 1996;335:1864-9.
29 Kollef MH, Shapiro SD, Silver P, St John RE, Prentice D, Sauer S, et al. A randomized, controlled trial of protocol-directed versus physician-directed weaning from mechanical ventilation. *Crit Care Med* 1997;25:567-74.
30 Marelich GP, Murin S, Battistella F, Inciardi J, Vierra T, Roby M. Protocol weaning of mechanical ventilation in medical and surgical patients by respiratory care practitioners and nurses: effect on weaning time and incidence of ventilator-associated pneumonia. *Chest* 2000;118:459-67.
31 Esteban A, Alia I, Gordo F, Fernandez R, Solsona JF, Vallverdu I, et al. Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. *Am J Respir Crit Care Med* 1997;156:459-65.
32 Esteban A, Alia I, Tobin MJ. Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. *Am J Respir Crit Care Med* 1999;159:512-8.
33 Perren A, Domenighetti G, Mauri S, Genini F, Vizzardi N. Protocol-directed weaning from mechanical ventilation: clinical outcome in patients randomized for a 30-minute and 120-minute trial with pressure support. *Intensive Care Med* 2002;28:1058-63.
34 Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med* 1999;27:2609-15.


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