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Noninvasive positive-pressure ventilation as a weaning strategy for intubated adults with respiratory failure.
Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD004127.
DOI: 10.1002/14651858.CD004127.pub3.

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TABLE OF CONTENTS

[Intervention Review]

Noninvasive positive-pressure ventilation as a weaning strategy for intubated adults with respiratory failure

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Editorial group: Cochrane Emergency and Critical Care Group.
Publication status and date: Edited (no change to conclusions), published in Issue 12, 2018.

Citation: Burns KEA, Meade MO, Premji A, Adhikari NKJ. Noninvasive positive-pressure ventilation as a weaning strategy for intubated adults with respiratory failure. *Cochrane Database of Systematic Reviews* 2013, Issue 12. Art. No.: CD004127. DOI: 10.1002/14651858.CD004127.pub3.

ABSTRACT

Background

Noninvasive positive-pressure ventilation (NPPV) provides ventilatory support without the need for an invasive airway. Interest has emerged in using NPPV to facilitate earlier removal of an endotracheal tube and to decrease complications associated with prolonged intubation.

Objectives

We evaluated studies in which invasively ventilated adults with respiratory failure of any cause (chronic obstructive pulmonary disease (COPD), non-COPD, postoperative, nonoperative) were weaned by means of early extubation followed by immediate application of NPPV or continued IPPV weaning. The primary objective was to determine whether the noninvasive positive-pressure ventilation (NPPV) strategy reduced all-cause mortality compared with invasive positive-pressure ventilation (IPPV) weaning. Secondary objectives were to ascertain differences between strategies in proportions of weaning failure and ventilator-associated pneumonia (VAP), intensive care unit (ICU) and hospital length of stay (LOS), total duration of mechanical ventilation, duration of mechanical support related to weaning, duration of endotracheal mechanical ventilation (ETMV), frequency of adverse events (related to weaning) and overall quality of life. We planned sensitivity and subgroup analyses to assess (1) the influence on mortality and VAP of excluding quasi-randomized trials, and (2) effects on mortality and weaning failure associated with different causes of respiratory failure (COPD vs. mixed populations).

Search methods

We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, Issue 5, 2013), MEDLINE (January 1966 to May 2013), EMBASE (January 1980 to May 2013), proceedings from four conferences, trial registration websites and personal files; we contacted authors to identify trials comparing NPPV versus conventional IPPV weaning.

Selection criteria

Randomized and quasi-randomized trials comparing early extubation with immediate application of NPPV versus IPPV weaning in intubated adults with respiratory failure.

Data collection and analysis

Two review authors independently assessed trial quality and abstracted data according to prespecified criteria. Sensitivity and subgroup analyses assessed (1) the impact of excluding quasi-randomized trials, and (2) the effects on selected outcomes noted with different causes of respiratory failure.

Main results

We identified 16 trials, predominantly of moderate to good quality, involving 994 participants, most with chronic obstructive pulmonary disease (COPD). Compared with IPPV weaning, NPPV weaning significantly decreased mortality. The benefits for mortality were significantly greater in trials enrolling exclusively participants with COPD (risk ratio (RR) 0.36, 95% confidence interval (CI) 0.24 to 0.56) versus mixed populations (RR 0.81, 95% CI 0.47 to 1.40). NPPV significantly reduced weaning failure (RR 0.63, 95% CI 0.42 to 0.96) and ventilator-associated pneumonia (RR 0.25, 95% CI 0.15 to 0.43); shortened length of stay in an intensive care unit (mean difference (MD) -5.59 days, 95% CI -7.90 to -3.28) and in hospital (MD -6.04 days, 95% CI -9.22 to -2.87); and decreased the total duration of ventilation (MD -5.64 days, 95% CI -9.50 to -1.77) and the duration of endotracheal mechanical ventilation (MD - 7.44 days, 95% CI -10.34 to -4.55) amidst significant heterogeneity. Noninvasive weaning also significantly reduced tracheostomy (RR 0.19, 95% CI 0.08 to 0.47) and reintubation (RR 0.65, 95% CI 0.44 to 0.97) rates. Noninvasive weaning had no effect on the duration of ventilation related to weaning. Exclusion of a single quasi-randomized trial did not alter these results. Subgroup analyses suggest that the benefits for mortality were significantly greater in trials enrolling exclusively participants with COPD versus mixed populations.

Authors' conclusions

Summary estimates from 16 trials of moderate to good quality that included predominantly participants with COPD suggest that a weaning strategy that includes NPPV may reduce rates of mortality and ventilator-associated pneumonia without increasing the risk of weaning failure or reintubation.

PLAIN LANGUAGE SUMMARY

Use of noninvasive ventilation (a mask ventilator) holds promise as a method to make it easier to remove adults from conventional ventilators.

Patients with acute respiratory failure frequently require endotracheal intubation and mechanical ventilation (invasive positive-pressure ventilation) to sustain life. Complications of mechanical ventilation include respiratory muscle weakness, upper airway injury, ventilator-associated pneumonia, sinusitis and associated death. For these reasons, it is important to minimize the duration of mechanical ventilation. Noninvasive positive-pressure ventilation is achieved with an oronasal, nasal or total face mask connected to a positive-pressure ventilator and does not require an indwelling artificial airway.

Results from 16 randomized controlled trials, predominantly of moderate to good quality, involving 994 selected participants, approximately two thirds with chronic obstructive pulmonary disease who had respiratory failure and were starting to breathe spontaneously, demonstrate that support with noninvasive ventilation can decrease death, weaning failure, pneumonia and length of stay in the intensive care unit and hospital. Noninvasive weaning also decreased the total duration of ventilation and the time spent on invasive ventilation, as well as the number of participants who received a tracheostomy. Although noninvasive weaning had no effect on the duration of mechanical ventilation related to weaning, it did not increase the reintubation rate. Insufficient data were available to assess its impact on quality of life. Noninvasive weaning significantly reduced mortality in chronic obstructive pulmonary disease studies versus mixed population studies.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Noninvasive versus invasive weaning for intubated adults with respiratory failure

Noninvasive versus invasive weaning for intubated adults with respiratory failure

Patient or population: intubated adults with respiratory failure
Settings:
Intervention: noninvasive versus invasive weaning

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Noninvasive versus invasive weaning				
Mortality—COPD	**Study population**		**RR 0.36** (0.24 to 0.56)	632 (9 studies)	⊕⊕⊕⊖ **moderate**[1]	
	225 per 1000	**81 per 1000** (54 to 126)				
	Moderate					
	200 per 1000	**72 per 1000** (48 to 112)				
Mortality—mixed	**Study population**		**RR 0.81** (0.47 to 1.4)	362 (7 studies)	⊕⊕⊖⊖ **low**[1]	
	239 per 1000	**194 per 1000** (112 to 335)				
	Moderate					
	270 per 1000	**219 per 1000** (127 to 378)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1]Fewer than 300 events.
Test for subgroup differences (P = 0.02).

Summary of findings 2. Noninvasive versus invasive weaning for intubated adults with respiratory failure

Noninvasive versus invasive weaning for intubated adults with respiratory failure

Patient or population: patients with intubated adults with respiratory failure
Settings:
Intervention: Noninvasive versus invasive weaning

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Noninvasive versus invasive weaning				
Weaning failure	**Study population**		**RR 0.63** (0.42 to 0.96)	605 (8 studies)	⊕⊕⊕⊖ **moderate**[1]	
	362 per 1000	**228 per 1000** (152 to 348)				
	Moderate					
	327 per 1000	**206 per 1000** (137 to 314)				
Nosocomial pneumonia	**Study population**		**RR 0.25** (0.15 to 0.43)	953 (14 studies)	⊕⊕⊖⊖ **low**[2]	
	296 per 1000	**74 per 1000** (44 to 127)				
	Moderate					
	307 per 1000	**77 per 1000** (46 to 132)				
Average duration of ventila-		The mean average duration of ventilation related to weaning in the intervention groups was **0.25 lower**		645 (9 studies)	⊕⊕⊖⊖ **low**[3,4,5]	

tion related to weaning		(2.06 lower to 1.56 higher)			
Reintubation	**Study population**		**RR 0.65** (0.44 to 0.97)	789 (10 studies)	⊕⊕⊕⊖ **moderate**[1]
	310 per 1000	**202 per 1000** (137 to 301)			
	Moderate				
	286 per 1000	**186 per 1000** (126 to 277)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Less than 300 events
[2] RR 0.25 (95% CI 0.15 to 0.43)
[3] Impact of heterogeneity was considerable (I^2 =90%)
[4] 95% CI spans from a clinically important and significant increase or decrease
[5] Uncertain if estimates include non-survivors due to differential between group mortality (higher in control arm)

BACKGROUND

Description of the condition

Patients with acute respiratory failure (ARF) frequently require endotracheal intubation (ETI) and mechanical ventilation to sustain life. Although invasive ventilation is effective, it has been associated with the development of complications, including respiratory muscle weakness, upper airway pathology, ventilator-associated pneumonia (VAP) (Pingleton 1988) and sinusitis (Niederman 1984). VAP in turn is associated with increased morbidity and a trend toward increased mortality (Heyland 1999). For these reasons, minimizing the duration of invasive mechanical support is an important goal of critical care (MacIntyre 2001).

Description of the intervention

Noninvasive positive-pressure ventilation (NPPV) may provide a means of avoiding the need for or reducing the duration of invasive mechanical support for intubated patients with ARF. Unlike conventional invasive ventilation, NPPV is achieved with an oronasal, nasal or total face mask or a helmet connected to a ventilator and does not require an artificial airway. Through NPPV, one can (1) administer oxygen, (2) augment tidal volume and (3) apply extrinsic positive end-expiratory pressure (ePEEP) to counteract intrinsic positive end-expiratory pressure (iPEEP) (Appendini 1994). NPPV may provide partial ventilatory support to patients recovering from respiratory failure and who require ventilator support but have regained the ability to breathe spontaneously and can be extubated. NPPV has been shown to augment tidal volume, reduce breathing frequency, rest the muscles of respiration and improve gas exchange (Nava 1993). A small, prospective physiologic study of participants with chronic obstructive pulmonary disease (COPD) with hypercapneic respiratory failure who were not capable of fully autonomous breathing demonstrated that although physiologic and clinical responses to the delivery of noninvasive and invasive pressure support (PS) were similar (Vitacca 2001), significantly higher tidal volumes and lower dyspnoea scores were achieved with noninvasive PS (Vitacca 2001).

With acute exacerbation of COPD, the effectiveness of NPPV in decreasing mortality and ETI rates has been demonstrated in randomized trials and meta-analyses (Keenan 2003; Peter 2002). Data to support the use of NPPV in non-COPD participants with hypoxaemic respiratory failure are inconclusive at present (Keenan 2004). 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 noninvasive ventilation (Keenan 2011).

How the intervention might work

To mitigate the effects of complications associated with protracted invasive ventilation, investigators have explored the role of NPPV in weaning, that is, replacing invasive support with noninvasive support in patients who are ready to be weaned but are not ready to be immediately extubated. Because no tracheal prosthesis is used with the NPPV approach and the cough reflex is preserved, the risk for development of VAP is reduced (Antonelli 1998; Nourdine 1999). Additionally, weaning with NPPV may reduce the requirement for sedation (Rathgeber 1997), decrease psychological distress (Criner 1994) and preserve important functions, including speech and oral intake (Mehta 2001). NPPV has been identified by professional organizations, including the American College of Chest Physicians, American Association for Respiratory Care and American College of Critical Care Medicine, as a weaning modality that may decrease the duration of intubation and improve patient outcomes (Meade 2001). Potential limitations of the NPPV approach include forfeiture of a protected airway, desiccation of oral secretions and the ability of NPPV to provide only partial ventilatory support.

Why it is important to do this review

The first report to describe the successful use of NPPV in liberating participants with weaning failure from invasive positive-pressure ventilation (IPPV) was published in 1992 (Udwadia 1992). Thereafter, four uncontrolled, prospective studies were reported, in which participants with tracheostomies (Goodenberger 1992), participants with tracheostomies and translaryngeal airways (Restrick 1993) and those not meeting conventional discontinuation criteria (Gregoretti 1998; Kilger 1999) were weaned using NPPV. More recently, randomized controlled trials (RCTs) comparing the alternative weaning strategies have been published. The purpose of this review was to critically appraise, summarize and update information on the effects of NPPV weaning compared with IPPV weaning on important clinical outcomes, in light of new evidence derived from RCTs.

OBJECTIVES

We evaluated studies in which invasively ventilated adults with respiratory failure of any cause (COPD, non-COPD, postoperative, nonoperative) were weaned by means of early extubation followed by immediate application of NPPV or continued IPPV weaning.

1. The primary objective was to determine whether the noninvasive positive-pressure ventilation (NPPV) strategy reduced all-cause mortality compared with invasive positive-pressure ventilation (IPPV) weaning.
2. Secondary objectives were to ascertain differences between strategies in proportions of weaning failure and ventilator-associated pneumonia (VAP), intensive care unit (ICU) and hospital length of stay (LOS), total duration of mechanical ventilation, duration of mechanical support related to weaning, duration of endotracheal mechanical ventilation (ETMV), frequency of adverse events (related to weaning) and overall quality of life.

We planned sensitivity and subgroup analyses to assess (1) the influence on mortality and VAP of excluding quasi-randomized trials, and (2) effects on mortality and weaning failure associated with different causes of respiratory failure (COPD vs mixed populations).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized and quasi-randomized trials. We excluded trials that did not assess the role of NPPV and IPPV as weaning strategies and studies that compared NPPV and IPPV in the immediate postoperative setting (requiring discontinuation) or after unplanned extubation. Further, we excluded studies that compared the application of NPPV with supplemental oxygen

versus unassisted oxygen to prevent respiratory failure and reintubation after elective or unplanned extubation. We also excluded studies that evaluated exclusively tracheostomized participants. We permitted studies conducted outside the ICU setting.

Types of participants

Adults receiving IPPV for ARF or acute-on-chronic respiratory failure of any cause (COPD, non-COPD, postoperative, nonoperative) who were intubated for at least 24 hours were eligible for inclusion. We used authors' definitions of respiratory failure.

Types of interventions

A strategy of sequential extubation and weaning with NPPV was compared with a strategy of weaning using IPPV.

Types of outcome measures

Primary outcomes

The primary outcome was all-cause mortality, as reported at specific time points by study authors.

Secondary outcomes

Secondary outcomes included the following.

1. Weaning failure (the reinitiation of mechanical support after discontinuation, or the requirement for protracted mechanical support).
2. VAP (according to study authors' definitions of VAP).
3. ICU LOS.
4. Hospital LOS.
5. Total duration of mechanical ventilation (defined as the total number of days the participant required mechanical support—invasive or noninvasive).
6. Duration of ventilation related to weaning (defined as the time from randomization to discontinuation of support, death or study withdrawal or the time until a decision was made to institute home ventilation).
7. Duration of ETMV (defined as the time wherein mechanical ventilation was delivered through an artificial airway).
8. Adverse events related to weaning (including reintubation, tracheostomy, cutaneous irritation, nasal abrasions, gastric distension, general medical and specific complications such as sinusitis, arrhythmias, sepsis, pneumonia and barotrauma).
9. Quality of life (as assessed by study authors).

Search methods for identification of studies

Electronic searches

We used the standard strategy of the Cochrane Anaesthesia Review Group. We searched the Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library* 2013, Issue 5; see Appendix 1); MEDLINE via Ovid SP (January 1966 to May 2013; see Appendix 2); and EMBASE via Ovid SP (January 1980 to May 2013; see Appendix 3) to look for RCTs comparing NPPV and IPPV weaning strategies. No language restrictions were applied. To identify RCTs, we combined the MEDLINE search strategy with the Cochrane highly sensitive search strategy for identifying randomized trials in MEDLINE, as delineated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Searching other resources

We reviewed the bibliographies of retrieved articles and conference proceedings from the four international meetings published in the*American Journal of Respiratory and Critical Care Medicine*, *Intensive Care Medicine*, *Critical Care Medicine* and *Chest* (January 1995 to May 2013) to identify potentially relevant trials. Finally, we searched for ongoing trials on the websites www.controlled-trials.com and http://clinicaltrials.gov.

Data collection and analysis

Two review authors (KEAB, NKJA) independently screened citations, evaluated methodologic quality and abstracted data.

Selection of studies

We assessed trials on the basis of title and abstract. We retrieved potentially eligible trials in full text. We resolved disagreements regarding study selection and data abstraction by consensus or by arbitration with a third review author (MOM).

Data extraction and management

Data on the types of participants, interventions and outcomes included in each trial were extracted using a standardized data extraction form.

Assessment of risk of bias in included studies

The quality of all included trials was assessed by two review authors (KEAB, NKJK), both independently and in duplicate. For each study, we recorded the use of true randomization and the use of concealed allocation to minimize selection bias. Additionally, we evaluated reports of randomized trials for completeness of outcome data and selective outcomes reporting to assess for attrition and reporting biases, respectively. The two review authors evaluated each quality assessment independently and resolved disagreements through discussion and electronic email.

In detail, we judged study quality on the basis of the following (Higgins 2011).

1. Was sequence generation truly random?

Adequate sequence generation included reference to a random number table, use of a computer random number generator, coin tossing, shuffling of cards or envelopes, throwing of dice, drawing of lots or minimization.

2. Was knowledge of the allocated interventions adequately prevented during the study?

Adequate allocation concealment included central randomization (e.g. allocation by a central office unaware of participant characteristics unless based on stratification), such as an on-site computer system combined with allocation sequence kept in a locked unreadable computer file accessed only after the characteristics of an enrolled participant were entered; sequentially numbered, sealed, opaque envelopes; or another similar approach to ensure that the person generating the allocation sequence did not administer it.

3. Were withdrawals described, and did they occur with similar frequency in intervention and control groups?

4. Were reports of the study free of the suggestion of selective outcome reporting?

We assigned a judgement related to the risk of bias for each domain as follows.

- 'yes' (criteria appropriately applied and described in the report or acknowledged from the primary author of the study).
- 'unclear' (criteria not described or impossible to acquire from the author).
- 'no' (criteria inappropriately applied).

A judgement of 'Yes' indicated a low risk of bias, 'No' indicated a high risk of bias and 'Unclear' indicated an unknown or unclear risk of bias.

We used the principles of the GRADE system (Guyatt 2008) to assess the quality of the body of evidence in our review associated with specific outcomes (weaning time, time to successful extubation, time to first SBT and first successful SBT, mortality, total duration of mechanical ventilation, ICU length of stay and reintubation) and constructed Summary of findings for the main comparison; and Summary of findings table 2 (SoF tables) using the GRADE software (Higgins 2011). The GRADE approach appraised the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Assessment of the quality of a body of evidence considered within-study risk of bias (methodologic quality), directness of the evidence, heterogeneity of the data, precision of the effect estimates and risk of publication bias.

Measures of treatment effect

In pooled analyses, we used proportions for binary outcomes and preferentially used mean and standard deviation, when reported or available through correspondence with authors. Continuous outcomes are reported in days. We pooled categorical and continuous data using risk ratio (RR) and mean difference (MD) as respective summary estimates of effect.

Unit of analysis issues

Summary estimates of individual participants randomly assigned to the same intervention in the included trials constitute the unit of analysis in this review. For one trial with three arms, we included the results of two arms relevant to our research question (Girault 2011).

Dealing with missing data

For published reports with insufficient or ambiguous information, we contacted the first study author, when feasible, to clarify study methods.

Assessment of heterogeneity

We evaluated heterogeneity with the Cochran Q statistic (Cochran 1954) using a threshold P value of less than 0.10 (Fleiss 1986). We assessed the impact of heterogeneity on outcomes using the I^2 measure (Higgins 2002). We considered an I^2 statistic threshold of 0% to 40%, 30% to 60%, 50% to 90% or $\geq$ 75% to represent between-study heterogeneity that might not be important, moderate, substantial or considerable, respectively (Higgins 2011).

Assessment of reporting biases

We assessed effects of publication bias on the mortality outcome by constructing and visually inspecting a funnel plot that compared the study estimate of effect (RR) with the standard error of the log RR, while recognizing that the absence of small, negative trials may overinflate the overall summary estimate of effect (Higgins 2011).

Data synthesis

We used random-effects (RE) models to pool data quantitatively, using Review Manager 5.1 software (RevMan 5.1), when studies were overall clinically similar. If a single outcome was reported at two different time points, we included the more protracted measurement in the pooled analyses.

Subgroup analysis and investigation of heterogeneity

We assessed the impact of the causes of respiratory failure (COPD vs mixed populations) and of studies enrolling at least 50% COPD participants versus less than 50% COPD participants on mortality and weaning failure. Based on identification of important differences in mortality between COPD and mixed populations and on the advice of the editorial team, we assessed the impact of the cause of respiratory failure on all outcomes post hoc. For these outcomes, we tested the difference in RR between subcategories using a Chi^2 test (Borenstein 2008). We considered $P < 0.05$ to be statistically significant.

Sensitivity analysis

A priori, we planned to assess the effects of excluding quasi-randomized studies on mortality and VAP outcomes.

RESULTS

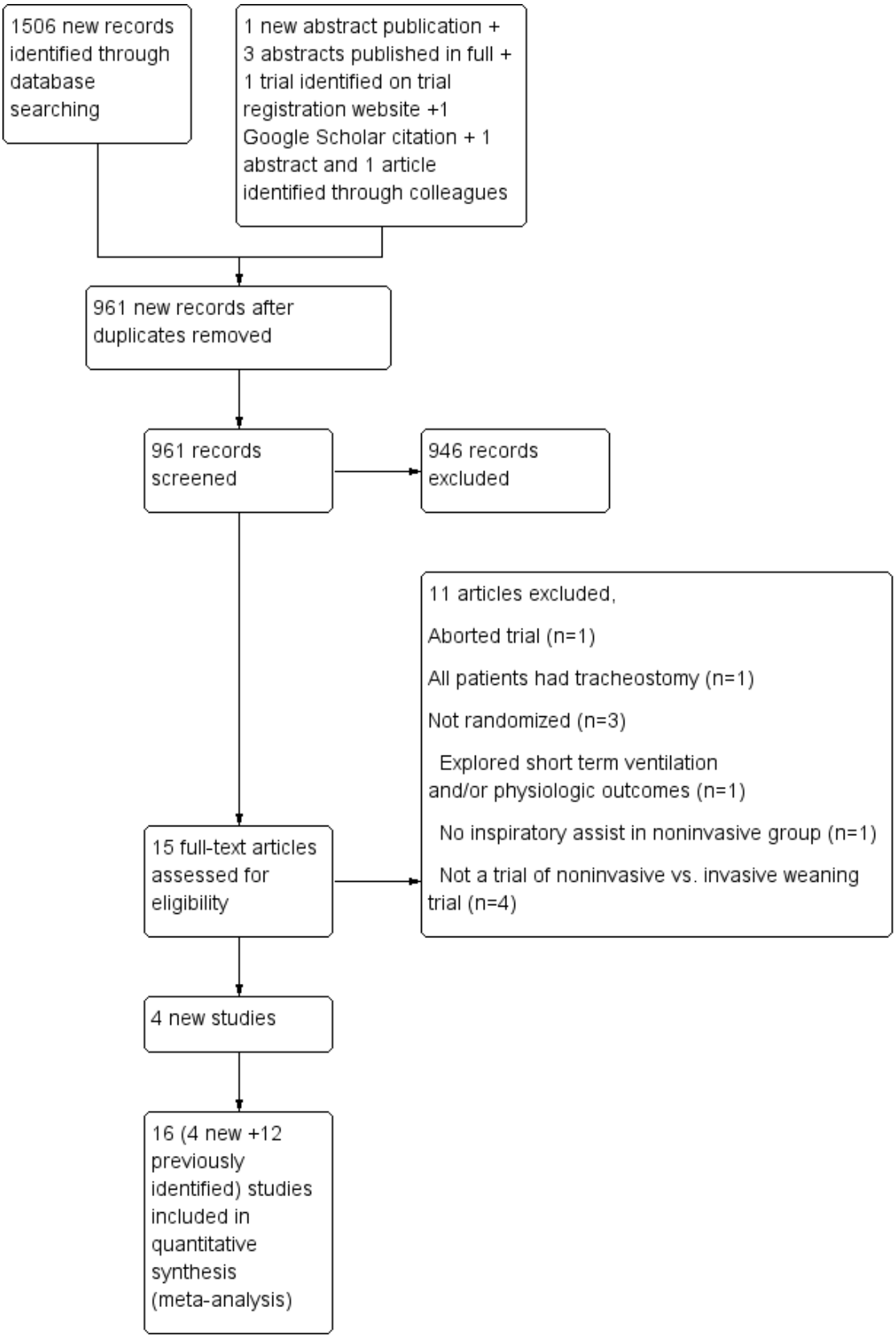
Description of studies

We identified a total of 16 trials, including 15 randomized trials (Ferrer 2003; Girault 1999; Girault 2011; Hill 2000; Nava 1998a; Prasad 2009; Rabie 2004; Rabie Agmy 2012; Tawfeek 2012; Trevisan 2008; Vaschetto 2012; Wang 2004; Wang 2005; Zheng 2005; Zou 2006) and one quasi-randomized trial (Chen 2001) that met our inclusion criteria (Table 1) (Characteristics of included studies).

Results of the search

We identified 1,506 records through an updated search (Figure 1). Of the 961 unique records, we assessed 14 new articles for eligibility.

Figure 1. Study flow diagram.



Included studies

Although we identified five additional trials from the updated search (Gao Smith 2006; Girault 2011; Rabie Agmy 2012; Tawfeek 2012; Vaschetto 2012), one author (Gao Smith 2006) confirmed that his trial was aborted after approximately eight participants were enrolled because of the need to fulfil a clinical requirement at another hospital. Consequently, we included in our updated review four newly identified trials (Girault 2011; Rabie Agmy 2012; Tawfeek 2012; Vaschetto 2012), in addition to the 12 previously identified trials. Full details of participants, interventions and outcomes for each trial are provided in the Characteristics of included studies table. Of the 16 included studies, two trials were published only in abstract form (Hill 2000; Rabie 2004), four trials were published in Chinese (Chen 2001; Wang 2004; Zheng 2005; Zou 2006), one trial was a doctoral dissertation, subsequently published in full (Prasad 2009), and another trial was labelled as a pilot RCT (Vaschetto 2012).

Excluded studies

In total, we excluded 20 trials (Celebi 2008; Du 2009; Duan 2012; Gao Smith 2006; Ishikawa 1997; Jiang 1999; Kilic 2008; Kruger 1998; Luo 2001; Matic 2007; Nava 2011; Radojevic 1997; Rong 2012; Rosinha 2002; Vargas 2012; Venkatram 2010; Wang 2000; Wang 2003; Yang 2009; Zheng 2011), including eight newly identified full publications, one aborted trial (Gao Smith 2006), one abstract publication (Vargas 2012) and one trial identified through a Google Scholar search (Rong 2012; see Characteristics of excluded studies). The two review authors achieved complete agreement on study selection.

Study participants were restricted to adults. Of the 16 RCTs identified, nine included exclusively participants with COPD (Chen 2001; Nava 1998a; Prasad 2009; Rabie 2004; Rabie Agmy 2012; Wang 2004; Wang 2005; Zheng 2005; Zou 2006) and seven trials included mixed or non-COPD populations (Ferrer 2003; Girault 1999; Girault 2011; Hill 2000; Tawfeek 2012; Trevisan 2008; Vaschetto 2012). Of the latter trials, COPD was diagnosed in approximately 75% of participants in three trials (Ferrer 2003; Girault 1999; Girault 2011), in approximately one third of participants in two trials (Hill 2000; Trevisan 2008) and in more than 20% of participants in another trial (Tawfeek 2012), and COPD served as an exclusion criterion in the final trial (Vaschetto 2012). Participants were considered difficult to wean in two trials (Girault 1999; Girault 2011) and as persistent weaning failures in another trial (Ferrer 2003). Four trials (Wang 2004; Wang 2005; Zheng 2005; Zou 2006) included participants with COPD with respiratory failure due to pulmonary infection.

Initial prerandomization ventilation strategies integrated predominantly volume-cycled ventilation strategies (Chen 2001; Ferrer 2003; Girault 1999; Girault 2011; Nava 1998a; Prasad 2009; Rabie 2004; Wang 2004; Wang 2005; Zou 2006) with or without concurrent or subsequent pressure support (PS). Screening for weaning eligibility was reported to occur daily in three trials (Ferrer 2003; Hill 2000; Rabie 2004) and daily after 48 hours of invasive ventilation in two trials (Girault 1999; Vaschetto 2012). Weaning candidates were identified after at least 24 hours (Prasad 2009); at 36 to 48 hours, including six to eight hours of paralysis (Nava 1998a); after at least 48 hours (Girault 1999; Girault 2011; Tawfeek 2012; Vaschetto 2012); at 48 to 60 hours (Chen 2001); at 72 hours, including six to eight hours of paralysis (Rabie 2004); or after three days (Ferrer 2003) of invasive ventilation. The four trials (Wang 2004; Wang 2005; Zheng 2005; Zou 2006) evaluating participants with COPD with pulmonary infection enrolled participants upon achievement of 'pulmonary infection control' (PIC) window criteria (Wang 2005; Zheng 2005; Zou 2006) or after infection control was achieved (Wang 2004). These criteria included an improved radiograph, temperature and white blood cell count (or percentage of neutrophils) and reduced secretion volume and tenacity (Wang 2004; Wang 2005; Zheng 2005; Zou 2006). Two trials also specified improved haemodynamics, expectoration and level of consciousness (Wang 2004; Zou 2006), and another (Wang 2005) specified minimum ventilator settings (synchronized intermittent mandatory ventilation (SIMV) rate of 10 to 12 breaths/min, PS of 10 to 12 cm H_2O). Eligibility for study inclusion and randomization required that participants meet predefined permissive weaning criteria (Chen 2001; Ferrer 2003; Girault 1999; Girault 2011; Nava 1998a; Prasad 2009; Rabie 2004; Rabie Agmy 2012; Tawfeek 2012; Trevisan 2008; Vaschetto 2012; Wang 2004; Wang 2005; Zheng 2005; Zou 2006) and that they fail a single 30-minute (Hill 2000; Trevisan 2008), one-hour (Nava 1998a) or two-hour (Girault 1999; Girault 2011; Prasad 2009; Rabie 2004; Rabie Agmy 2012; Tawfeek 2012) SBT, or a two-hour T-piece trial on three consecutive days (Ferrer 2003).

Weaning strategies

Invasive positive-pressure group

Participants in the control group were weaned using PS (Chen 2001; Ferrer 2003; Girault 1999; Girault 2011; Hill 2000; Nava 1998a; Prasad 2009; Rabie 2004; Rabie Agmy 2012; Vaschetto 2012; Zheng 2005), assist control (AC) (Ferrer 2003), SIMV with PS (Wang 2004; Wang 2005; Zou 2006) or SIMV alone (Tawfeek 2012). Initial support, after failure of an SBT, was titrated to achieve the prior $PaCO_2$ (Chen 2001; Nava 1998a; Prasad 2009; Rabie 2004; Tawfeek 2012), pH (Chen 2001; Nava 1998a; Prasad 2009; Rabie 2004; Tawfeek 2012) or respiratory rate (Chen 2001; Girault 1999; Hill 2000; Nava 1998a; Prasad 2009; Rabie 2004; Tawfeek 2012). In some trials, initial settings were adjusted to achieve specific flow rates (Girault 1999) or tidal volume (V_T) (Hill 2000). The level of PS was gradually reduced in three trials (Ferrer 2003; Girault 2011; Nava 1998a). One study each titrated PS by 2 cm H_2O every four hours to clinical tolerance, saturation and respiratory rate (Prasad 2009) or by 2 to 4 cm H_2O per day (Rabie 2004). Another trial decreased PS and positive end-expiratory pressure (PEEP) by 2 cm H_2O every two hours until a minimum of 8 and 10 cm H_2O, respectively, were attained and titrated support to PaO_2/FiO_2, $PaCO_2$ and pH (Vaschetto 2012).

Trials of spontaneous breathing (SB), using T-piece or continuous positive airway pressure (CPAP) < 5 cm H_2O or PS, were performed twice daily (Nava 1998a), daily (Ferrer 2003; Tawfeek 2012; Trevisan 2008) or at least once daily (Girault 2011). One study included at least two observation periods per day during PS weaning with optional SBTs (Girault 1999). Participants were considered weaned when (1) they remained stable for at least four hours on an SIMV rate of five breaths per minute with PS of 5 to 7 cm H_2O (Wang 2005); (2) blood gases were normalized and participants could spontaneously breathe for longer than three hours with low oxygen requirements ($FiO_2 \leq 0.40$), acceptable oxygen saturation ($SpO_2 \geq 90\%$) and a normal pH (≥ 7.35) (Wang 2004); or (3) when PS was titrated to ≤ 7 cm H_2O (Girault 2011), ≤ 8 cm H_2O (Zheng 2005) or ≤ 10 cm H_2O (Prasad 2009; Zou 2006) with PEEP of 5 cm

H_2O and satisfactory blood gases (Prasad 2009; Vaschetto 2012), saturations (Zheng 2005; Zou 2006) and respiratory rate (Prasad 2009; Vaschetto 2012; Zheng 2005; Zou 2006); a tidal volume of approximately 8 mL/kg (Zheng 2005; Zou 2006); and partial pressure of carbon dioxide ($PaCO_2$) between 45 and 60 mm Hg; or at baseline on low FiO_2 (Prasad 2009; Zheng 2005; Zou 2006) for longer than four hours (Zheng 2005; Zou 2006). A final trial considered participants to be weaned from invasive PS with arterial saturation ≥ 90% on an FiO_2 ≤ 40% with pH ≥ 7.35, RR < 35 breaths/min, haemodynamic stability and the absence of severe dyspnoea or depressed neurological status (Rabie 2004). To discontinue invasive ventilation, participants successfully completed a 30-minute SBT (Vaschetto 2012), a two-hour SBT (Ferrer 2003; Hill 2000) or a three-hour SBT (Chen 2001; Nava 1998a; Wang 2004), or two periods of observation with optional SBTs (Girault 1999). Three trials did not specify SBT duration (Girault 2011; Tawfeek 2012; Trevisan 2008).

Noninvasive ventilation group

Similar to invasive weaning, trials applied different noninvasive weaning protocols. After extubation, NPPV was administered in pressure mode in 13 trials (Chen 2001; Ferrer 2003; Girault 1999; Girault 2011; Hill 2000; Nava 1998a; Prasad 2009; Trevisan 2008; Vaschetto 2012; Wang 2004; Wang 2005; Zheng 2005; Zou 2006), of which six trials specified use of a spontaneous timed mode (Ferrer 2003; Girault 1999; Hill 2000; Prasad 2009; Rabie Agmy 2012; Zou 2006) or a flow mode (Girault 1999). Two trials (Girault 2011; Vaschetto 2012) did not specify the mode. Two studies used proportional assist ventilation (Rabie 2004; Tawfeek 2012). NPPV was preferentially delivered by face mask (Ferrer 2003; Girault 1999; Girault 2011; Hill 2000; Nava 1998a; Prasad 2009; Rabie 2004; Tawfeek 2012, Trevisan 2008; Wang 2005; Zheng 2005; Zou 2006) or nasal mask (Ferrer 2003; Girault 1999; Hill 2000; Rabie 2004; Zheng 2005; Zou 2006). One trial (Vaschetto 2012) used a helmet but also permitted use of full face and oronasal masks in rotation to improve tolerance to NPPV. Initial support was delivered continuously in seven studies (Chen 2001; Ferrer 2003; Hill 2000; Nava 1998a; Prasad 2009; Tawfeek 2012; Vaschetto 2012) and continuously initially and subsequently intermittently in one study (Girault 2011). Alternatively, NPPV was delivered intermittently in one study (Girault 1999) or for at least two (Zou 2006) or six (Girault 2011) hours during the initial application, and in one study until tolerated for 20 to 22 hours per day, spaced by periods of spontaneous ventilation with oxygen for meals and expectoration (Rabie 2004).

The level of support was gradually decreased (Tawfeek 2012; Zheng 2005; Zou 2006), and noninvasive ventilation time was gradually reduced (Zheng 2005; Zou 2006). Some trials permitted fixed or gradually increasing periods of spontaneous breathing (Ferrer 2003; Girault 1999; Hill 2000; Nava 1998a; Rabie 2004), with at least two trials (Nava 1998a; Rabie 2004) specifying two periods of spontaneous breathing per day. Other trials enabled spontaneous breathing when selected criteria were met (Vaschetto 2012) or intermittently between NPPV periods (Girault 2011). In some trials, clinicians titrated PS by 2 cm H_2O every two (Vaschetto 2012) or four (Prasad 2009) hours until PS and PEEP targets were achieved (Vaschetto 2012) or by 2 to 4 cm H_2O each day (Rabie 2004), according to participant tolerance. In one trial (Vaschetto 2012), the goal of the weaning protocol was specified as maintaining PaO_2/FiO_2 ≥ 225, $PaCO_2$ ≤ 50 mm Hg and pH ≥ 7.35. In some trials, clinicians decreased the levels of inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) to 8 and 4 cm H_2O, respectively (Prasad 2009). In other trials, IPAP was reduced to < 10 cm H_2O (with NPPV applied for less than two hours per day) (Zheng 2005; Zou 2006), or until the difference between IPAP and EPAP was ≤ 5 cm H_2O (Wang 2005). Still other trials considered participants to be weaned from noninvasive support when arterial saturations were ≥ 90% on an FiO_2 ≤ 40% with pH ≥ 7.35, RR < 35 breaths/min, haemodynamic stability and absence of severe dyspnoea or depressed neurological status (Rabie 2004), or according to blood gases, clinical status or mechanical ventilation parameters (Girault 2011; Vaschetto 2012; Wang 2004). One trial (Girault 2011) specified the need for daily NPPV for less than six hours or respiratory stability with standard oxygen therapy for at least 12 hours with arterial blood gases (ABGs): PaO_2 ≥ 64 mm Hg with pH ≥ 7.35 and $PaCO_2$ ≤ 60 mm Hg. Criteria for discontinuing noninvasive support included successful completion of a three-hour (Chen 2001; Nava 1998a), a two-hour (Hill 2000) or a 30-minute (Vaschetto 2012) period of spontaneous breathing, a period of observation of undetermined duration (Girault 2011) or at least two periods of spontaneous breathing observed by an attending physician (Girault 1999). One trial (Tawfeek 2012) did not conduct postrandomization periods of spontaneous breathing.

Risk of bias in included studies

See Figure 2 and Figure 3.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

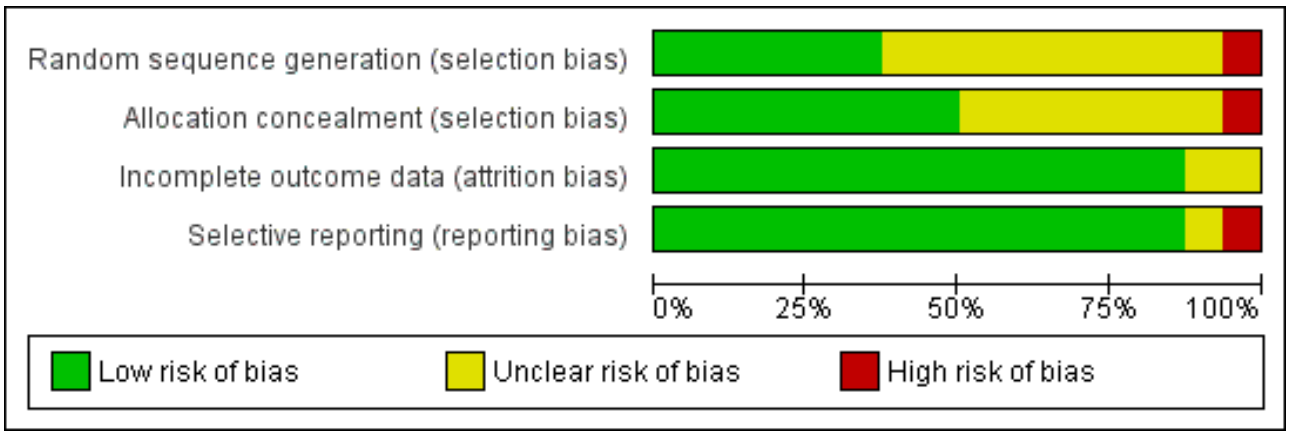
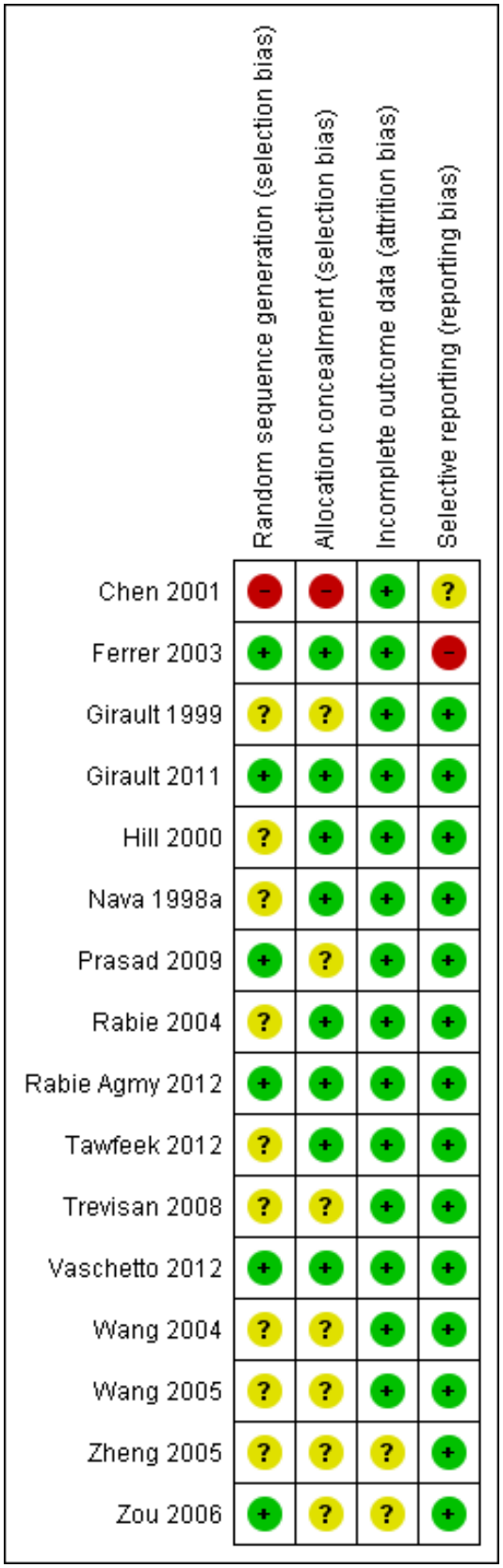


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

In most trials included in this review (Characteristics of included studies), allocation to treatment group was by random assignment, with one quasi-randomized trial allocating participants according to hospital admission order (Chen 2001). To generate randomization sequences, trials reported use of computer-generated random tables at each centre (Ferrer 2003), a computer-generated randomization table using variable blocks of four (Girault 2011), computer-generated randomization (Rabie Agmy 2012), Kendall and Babington tables (Prasad 2009), a table of random numbers held by an investigator not involved with study enrolment (Vaschetto 2012) and a digital table (Zou 2006). The remaining trials (Girault 1999; Hill 2000; Nava 1998a; Rabie 2004; Tawfeek 2012; Trevisan 2008; Wang 2004; Wang 2005; Zheng 2005) did not provide specific information regarding sequence generation.

To conceal allocation, trials reported using sealed envelopes (Trevisan 2008), opaque envelopes (Girault 1999) or sealed, opaque envelopes (Girault 2011; Hill 2000). Three trials reported using sealed, opaque, sequentially numbered envelopes (Nava 1998a; Tawfeek 2012 Vaschetto 2012). One study used a computer-generated randomization list held by investigators not involved in clinical decisions (Ferrer 2003). The method of allocation concealment was not specified in five trials (Prasad 2009; Wang 2004; Wang 2005; Zheng 2005; Zou 2006) and was confirmed to be concealed through correspondence with one study author for two other trials (Rabie 2004; Rabie Agmy 2012).

Blinding

Because of the nature of the interventions, blinding of caregivers and participants was not possible; however, one trial (Hill 2000) blinded individuals participating in data collection and analysis.

Incomplete outcome data

We assessed for completeness of outcome data in publications by inspecting denominators, when provided. In two trials (Zheng 2005; Zou 2006), denominators were not provided in binary outcomes to ensure complete outcomes reporting.

Selective reporting

Selective outcomes reporting was judged to be unclear in one trial (Chen 2001), which reported clinically important outcomes but did not specify primary and secondary outcomes. Another trial (Ferrer 2003) did not report the proportions of weaning successes and failures in a full trial publication but reported this outcome in a smaller number of participants in an earlier abstract publication, with the authors affirming that they did not continue to collect data on this outcome.

Other potential sources of bias

We did not evaluate other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Noninvasive versus invasive weaning for intubated adults with respiratory failure; **Summary of findings 2** Noninvasive versus invasive weaning for intubated adults with respiratory failure

Eleven study authors (Ferrer 2003; Girault 1999; Girault 2011; Hill 2000; Nava 1998a; Prasad 2009; Rabie 2004; Rabie Agmy 2012; Trevisan 2008; Vaschetto 2012; Wang 2005; Zou 2006) confirmed and supplemented information related to study methods. Overall, the included trials were of moderate to good quality (Figure 2; Figure 3).

Mortality

Sixteen trials involving 994 participants provided mortality data. Mortality was reported at 30 days (Prasad 2009; Tawfeek 2012), at 60 days (Nava 1998a), at 90 days (Ferrer 2003; Girault 1999), at ICU (Girault 2011; Vaschetto 2012) and hospital discharge (Girault 1999; Rabie 2004; Rabie Agmy 2012; Trevisan 2008; Vaschetto 2012; Wang 2005; Zheng 2005; Zou 2006) and at an undefined time point (Chen 2001; Hill 2000; Wang 2004). Strong evidence indicated that NPPV weaning reduced mortality (RR 0.53, 95% confidence interval (CI) 0.36 to 0.80, P = 0.002) with moderate heterogeneity (I^2 = 37%, P = 0.07). We noted a significant beneficial effect (Chi^2 = 5.12, P = 0.02) of noninvasive weaning on mortality in participants with COPD (nine trials) compared with mixed populations (seven trials) (RR 0.36, 95% CI 0.24 to 0.56, P < 0.00001; RR 0.81, 95% CI 0.47 to 1.40, P = 0.45, respectively; see Analysis 1.1; Summary of findings for the main comparison).

Proportion of weaning failures

Eight trials, involving 605 participants, reported the proportions of participants successfully weaned (Girault 1999; Girault 2011; Hill 2000; Nava 1998a; Rabie 2004; Rabie Agmy 2012; Tawfeek 2012; Vaschetto 2012). Successful weaning was not defined in two studies (Girault 2011; Rabie 2004) and was defined in two studies as not requiring initiation of NPPV or reintubation within 72 hours (Nava 1998a; Tawfeek 2012) or as not requiring reintubation within 48 hours (Hill 2000). Another trial (Girault 1999) defined weaning failure as the need for reintubation by day five after extubation or, when extubation was not possible, within five days of initiation of weaning efforts in the IPPV group. In this trial (Girault 1999), all participants with weaning failure were reintubated within five days. Successful weaning was defined as the absence of reintubation within three days after extubation (Tawfeek 2012) or, if reintubation or noninvasive ventilation was not required, within 72 hours of suspension of ventilation (Rabie Agmy 2012). Similarly, Vaschetto et al (Vaschetto 2012) defined extubation failure as the inability to sustain spontaneous unassisted breathing for 48 consecutive hours without development of respiratory failure requiring ventilatory support (invasive or noninvasive). With moderate heterogeneity (I^2 = 39%, P = 0.12), the pooled data demonstrated a significant reduction in the proportion of weaning failures with noninvasive weaning (RR 0.63, 95% CI 0.42 to 0.96, P = 0.03). Although summary estimates of effect on weaning failure suggested greater benefit in three trials evaluating participants with COPD (RR 0.52, 95% CI 0.36 to 0.74, P = 0.0002) versus five trials involving mixed populations (RR 0.73, 95% CI 0.35 to 1.51, P = 0.40), between-group differences were not significant (Chi^2 = 0.71, P = 0.40; see Analysis 2.1; Summary of findings table 2).

Ventilator-associated pneumonia

Although the proportions of participants developing VAP were reported in 14 trials (Chen 2001; Ferrer 2003; Girault 1999; Girault 2011; Nava 1998a; Prasad 2009; Rabie 2004; Rabie Agmy 2012; Tawfeek 2012; Trevisan 2008; Wang 2004; Wang 2005; Zheng 2005;

Zou 2006) involving 953 participants, criteria for the diagnosis of VAP during weaning were provided in ten trials (Chen 2001; Ferrer 2003; Nava 1998a; Prasad 2009; Tawfeek 2012; Trevisan 2008; Wang 2004; Wang 2005; Zheng 2005; Zou 2006). The pooled estimate demonstrated a beneficial effect of noninvasive weaning in reducing VAP (RR 0.25, 95% CI 0.15 to 0.43, P < 0.00001), with moderate heterogeneity (I^2 = 38%, P = 0.07; see Analysis 3.1; Summary of findings table 2). The effect on VAP was not different in participants with COPD compared with mixed populations (P value (subgroup differences) = 0.31).

Intensive care unit length of stay

Thirteen trials (Ferrer 2003; Girault 1999; Girault 2011; Nava 1998a; Prasad 2009; Rabie 2004; Rabie Agmy 2012; Trevisan 2008; Vaschetto 2012; Wang 2004; Wang 2005; Zheng 2005; Zou 2006) involving 907 participants evaluated ICU LOS. The aggregate data revealed a significant reduction in ICU LOS of five days favouring noninvasive weaning (MD -5.59 days, 95% CI -7.90 to -3.28, P < 0.00001) amidst considerable heterogeneity (I^2 = 77%, P < 0.00001; see Analysis 4.1). The effect on ICU stay was not different in participants with COPD versus mixed populations (P value (subgroup differences) = 0.14).

Hospital length of stay

Ten trials including 803 participants reported hospital LOS (Chen 2001; Ferrer 2003; Girault 1999; Girault 2011; Rabie 2004; Rabie Agmy 2012; Trevisan 2008; Wang 2005; Zheng 2005; Zou 2006). These trials noted a significant reduction in hospital LOS of six days (MD -6.04 days, 95% CI -9.22 to -2.87, P = 0.0002) amidst considerable heterogeneity (I^2 = 78%, P < 0.00001; see Analysis 5.1). The effect on hospital stay was not different in participants with COPD versus mixed populations (P value (subgroup differences) = 0.39).

Mean total duration of mechanical ventilation

We found significant reductions in the total duration of mechanical ventilation in seven trials that included 385 participants (Ferrer 2003; Nava 1998a; Trevisan 2008; Wang 2004; Wang 2005; Zheng 2005; Zou 2006) (MD -5.64 days, 95% CI -9.50 to -1.77, P = 0.004), with considerable heterogeneity (I^2 = 86%, P < 0.00001; see Analysis 6.1). The effect on total duration of mechanical ventilation was not different in participants with COPD versus mixed populations (P value (subgroup differences) = 0.89).

Mean duration of ventilation related to weaning

We found no effect of noninvasive weaning on the duration of mechanical ventilation related to weaning in nine trials involving 645 participants (Chen 2001; Ferrer 2003; Girault 1999; Girault 2011; Prasad 2009; Rabie 2004; Rabie Agmy 2012; Trevisan 2008; Vaschetto 2012) (MD -0.25 days, 95% CI -2.06 to 1.56, P = 0.79), with considerable heterogeneity (I^2 = 90%, P < 0.00001; see Analysis 7.1; Summary of findings table 2). The effect on duration of ventilation related to weaning was not different in participants with COPD versus mixed populations (P value (subgroup differences) = 0.48).

Mean duration of endotracheal mechanical ventilation

Twelve trials (Ferrer 2003; Girault 1999; Hill 2000; Prasad 2009; Rabie 2004; Rabie Agmy 2012; Tawfeek 2012; Vaschetto 2012; Wang 2004; Wang 2005; Zheng 2005; Zou 2006) that included 717 participants reported the duration of ETMV. In the presence of considerable heterogeneity (I^2 = 87%, P < 0.00001), the summary estimate demonstrated a significant decrease in the duration of ETMV with noninvasive weaning (MD -7.44 days, 95% CI -10.34 to -4.55, P < 0.00001; see Analysis 8.1). The effect on duration of ETMV was not different in participants with COPD versus mixed populations (P-value (subgroup differences) = 0.81).

Adverse events

Variability in selection and reporting of adverse events in individual trials precluded pooling of most data.

Reintubation

The rate of reintubation was reported separately from the proportion of weaning failures in ten trials (Ferrer 2003; Girault 1999; Girault 2011; Hill 2000; Rabie Agmy 2012; Tawfeek 2012; Trevisan 2008; Vaschetto 2012; Wang 2005; Zou 2006) involving 789 participants. The pooled estimate supported a significant reduction in reintubation rate with noninvasive weaning (RR 0.65, 95% CI 0.44 to 0.97, P = 0.03), with moderate heterogeneity (I^2 = 41%, P = 0.08; see Analysis 9.1; Summary of findings table 2). The effect on reintubation rates was not different in participants with COPD versus mixed populations (P value (subgroup differences) = 0.13).

Arrhythmia

The pooled results of three trials (Girault 1999; Girault 2011; Prasad 2009), including 201 participants, demonstrated no effect of noninvasive weaning on development of arrhythmias (RR 0.89, 95% CI 0.34, 2.34, P = 0.81), in the absence of heterogeneity (I^2 = 0%, P = 0.63; see Analysis 10.1). The effect on arrhythmia rates was not different in participants with COPD versus mixed populations (P value (subgroup differences) = 0.44).

Tracheostomy

Seven trials involving 572 participants (Ferrer 2003; Girault 1999; Girault 2011; Rabie Agmy 2012; Tawfeek 2012; Trevisan 2008; Vaschetto 2012) reported the requirement for tracheostomy. The pooled estimated demonstrated a significant reduction in the rate of tracheostomy (RR 0.19, 95% CI 0.08 to 0.47, P = 0.0004), in the presence of unimportant heterogeneity (I^2 = 10%, P = 0.35; see Analysis 11.1). The effect on rate of tracheostomy was not different in participants with COPD versus mixed populations (P value (subgroup differences) = 0.22).

Quality of life

Quality of life was not reported.

Sensitivity analysis

Exclusion of a quasi-randomized trial (Chen 2001) supported significant reductions in pooled mortality (RR 0.60, 95% CI 0.40 to 0.90, P = 0.01) and VAP (RR 0.27, 95% CI 0.16 to 0.45, P < 0.00001) favouring the noninvasive approach to weaning (see Analysis 12.1; Analysis 12.2).

Subgroup analyses

Similarly, subgroup analysis comparing trials that enrolled at least 50% COPD participants (12 trials) versus those enrolling less than 50% COPD participants (four trials) supported a trend towards noninvasive weaning (Chi^2 = 2.39, P = 0.12) leading to reduced

mortality in trials that enrolled predominantly COPD participants (RR 0.47, 95% CI 0.29 to 0.76, P = 0.002; RR 0.86, 95% CI 0.47 to 1.58, P = 0.63; see Analysis 13.1).

We found a nonsignificant effect (Chi^2 = 0.15, P = 0.70) of noninvasive weaning on between-group differences in weaning failure in five trials enrolling at least 50% COPD participants compared with mixed population (three trials) subcategories (RR 0.68, 95% CI 0.46 to 1.01, P = 0.06; RR 0.51, 95% CI 0.12 to 2.18, P = 0.36, respectively; see Analysis 14.1).

Publication bias

Visual inspection of a funnel plot comparing study estimate of effect (RR) with standard error of the log RR for mortality did not reveal important asymmetry.

DISCUSSION

Summary of main results

We identified 16 trials comparing NPPV and IPPV weaning strategies among 994 participants, most with COPD. Compared with IPPV, NPPV significantly decreased mortality (Summary of findings for the main comparison), weaning failure and VAP (Summary of findings table 2). Amidst significant heterogeneity, NPPV weaning also significantly reduced ICU and hospital LOS, total duration of mechanical ventilation and duration of invasive ventilation. Although noninvasive weaning significantly reduced tracheostomy and reintubation rates, it had no effect on the duration of mechanical ventilation related to weaning (Summary of findings table 2). Exclusion of a single quasi-randomized trial supported statistically significant reductions in mortality and VAP favouring NPPV. Subgroup analyses suggested that benefits of the noninvasive approach to weaning in terms of mortality were significantly greater in trials enrolling exclusively COPD participants compared with those enrolling mixed populations. Summary estimates from 16 trials of moderate to good quality, including predominantly participants with COPD, demonstrated a positive effect of noninvasive weaning on mortality and VAP without increased risk of weaning failure or reintubation.

Overall completeness and applicability of evidence

Most studies in our review included participants exclusively (Chen 2001; Nava 1998a; Prasad 2009; Rabie 2004; Rabie Agmy 2012; Wang 2004; Wang 2005; Zheng 2005; Zou 2006) or predominantly (Ferrer 2003; Girault 1999) diagnosed with COPD. Patients with chronic airflow limitation may be ideally suited to NPPV given its ability to offset respiratory muscle fatigue and tachypnoea, augment tidal volume and reduce iPEEP. Subgroup analyses suggested greater benefit with noninvasive weaning in COPD participants, with statistical tests of subgroup effects achieving statistical significance. Notwithstanding, inferences from subgroup analyses may be limited by inclusion of COPD participants in mixed population studies and by the small number of trials comparing alternative weaning strategies in participants with respiratory failure of other causes. Whether other causes of respiratory failure are as amenable as COPD to noninvasive weaning remains to be determined in a single, adequately powered RCT.

This review was strengthened by an extensive search for relevant trials. We screened citations and abstracted data independently and in duplicate, and we corresponded with investigators to clarify study methods and outcomes reporting, when needed. Pooling of results in a meta-analysis implicitly assumes that the included studies are sufficiently similar with respect to populations, study interventions, outcomes and methodologic quality that one could reasonably expect a comparable underlying treatment effect. To this end, we exclusively used random-effects models for pooling data, which take into consideration both between-study and within-study variation. A priori, we planned to perform sensitivity and subgroup analyses to explain anticipated differences among study results.

Quality of the evidence

Studies included in this meta-analysis varied in the methods used to identify weaning candidates and to titrate and discontinue mechanical support. Multidisciplinary protocols used to identify weaning candidates and to perform daily SBTs reduce the duration of mechanical ventilation (Ely 1996; Ely 2001; Esteban 1997; Esteban 1999; Kollef 1997; Marelich 2000; Perren 2002). For patients failing an SBT, PS or intermittent or once-daily SBTs are favoured over SIMV to facilitate discontinuation of support (Brochard 1994; Butler 1999; Esen 1992; Esteban 1995; Jounieaux 1994; Tomlinson 1989). Although criteria used to identify candidates for an SBT or for weaning were used in 11 trials, only three trials screened daily for SBT readiness. In addition, four trials each conducted prerandomization SBTs and assessed for resolution of pulmonary infection to identify weaning readiness. The latter strategy represents a novel approach to identifying weaning candidates in selected populations and prioritizes identifying the cause of respiratory failure (bronchopulmonary infection) over meeting conventional weaning criteria. Methods for identifying weaning candidates may have an impact on study estimates of the duration of ventilation; however, these prerandomization study design considerations 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 (noninvasive strategy) or SBTs (invasive strategy) were permitted were variably reported among the included trials and represent important postrandomization study design considerations that could bias estimates of the duration of ventilation in unblinded weaning trials. Trials also varied in their selection and reporting of outcomes. An additional important study design consideration for weaning trials that could have an impact on the duration of ventilation is sedation administration (Brook 1999). Only one trial (Hill 2000) in our review used a sedation protocol. Overall, most trials in this review were of moderate quality; three trials were evaluated to be at low risk of bias and two trials were considered to be at high risk of bias.

Potential biases in the review process

In summary estimates, we found that noninvasive weaning significantly reduced mortality, ICU and hospital LOS and total duration of mechanical ventilation; these findings are consistent with and may be due to reduced VAP. However, we cannot ignore the fact that having direct access to respiratory secretions in invasively weaned participants may have resulted in detection bias by enhancing VAP detection in this group compared with the noninvasively weaned group. Inspection of control group rates of VAP in our review shows that they varied widely, ranging from 6.3% (Girault 1999) to 59.1% (Ferrer 2003). Similarly, control group mortality rates in our review ranged from 11.1% (Hill 2000; Rabie 2004) to 60.0% (Prasad 2009). Across trials, 173

total mortality events and 174 total VAP events were reported. Disparate control group mortality and VAP event rates, potential for detection bias in assessment of VAP, total of less than several hundred mortality VAP events (Devereaux 2004; Thorlund 2011) and selection and reporting of continuous outcomes limit the strength of inferences that can be made from this review. In addition, although estimates of the impact of heterogeneity associated with pooled estimates of mortality, VAP and reintubation were considered moderate, estimates associated with most continuous outcomes (ICU and hospital LOS, total duration of mechanical ventilation and duration of endotracheal mechanical intubation) were considerable. To this end, we considered estimates of the impact of heterogeneity to be unimportant (Higgins 2011) for only two outcomes (arrhythmia and tracheostomy rates), which significantly favoured noninvasive weaning. Finally, we noted effect modification with NPPV weaning in subgroup analysis of mortality but not for other outcomes. This finding may reflect differences in the populations studied, physiological benefits of NPPV in COPD participants, ecological bias (findings at the trial level driven by some other differences between trials, such as quality, that may not be confirmed by a within-trial subgroup analysis), lack of robustness of the mortality subgroup analysis or lack of power in the other subgroup analyses conducted.

Agreements and disagreements with other studies or reviews

In their efforts to optimize the time 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 (Epstein 1997). Noninvasive weaning, by providing ventilatory support without an artificial airway, offers a potential solution to this trade-off. Summary estimates from 16 trials of moderate to good quality, most with COPD participants, demonstrated a positive effect of NPPV weaning on mortality and VAP without increased risk of weaning failure or reintubation.

Notwithstanding these data, clinicians may be reluctant to incorporate noninvasive weaning into clinical practice because of the need to surrender a protected airway, concerns regarding the ventilatory support that can be provided with NPPV and increased risk for developing VAP if reintubation is required (Pawar 2003). Promising findings associated with noninvasive weaning require confirmation in a single, large, adequately powered RCT. The optimal timing for transitioning patients to NPPV for weaning remains to be determined. Additionally, whether other causes of respiratory failure are as amenable as COPD to noninvasive weaning remains to be elucidated.

AUTHORS' CONCLUSIONS

Implications for practice

Current trials of noninvasive weaning, mainly small trials most with COPD, show near-consistent positive effects on mortality and VAP without increased risk of weaning failure and reintubation. Although use of NPPV to wean participants with COPD is associated with highly encouraging net clinical benefit (number needed to treat for an additional beneficial outcome (to prevent death) of 8.9 in all participants and 6.5 in the COPD subgroup), most evidence has been obtained from small randomized trials. Given the potential for small event rates to be misleading when results from multiple small RCTs are pooled, additional evidence is required from a large, adequately powered RCT before we can recommend the routine use of NPPV as an adjunct for weaning patients from invasive mechanical ventilation. If consideration is given to adopting this approach to wean patients, we suggest that it be preferentially used in patients with COPD and in highly monitored environments at expert centres.

Implications for research

A well-designed, adequately powered RCT with explicitly defined end points that can be used to compare the alternative approaches to weaning is justified.

Several unanswered questions remain regarding the role of noninvasive weaning in the ICU. These include the following.

1. Does the NPPV strategy decrease the duration of ventilation related to weaning?
2. Does the cause of respiratory failure (COPD vs other) influence the effectiveness of noninvasive weaning?
3. Does illness severity at the time of randomization or duration of mechanical ventilation before randomization influence the effectiveness of noninvasive weaning?
4. What are the consequences of reintubation? Do important trade-offs exist between weaning failure and consequences of reintubation (VAP, mortality and ICU LOS)?
5. Can the same potential benefits be realized in diverse populations and at other centres without local expertise in noninvasive weaning?
6. What is the effect of noninvasive weaning on quality of life?

To address these questions, future trials should consider incorporation of:

1. stratification based on cause of respiratory failure (COPD, non-COPD);
2. daily screening for participant identification;
3. incorporation of weaning guidelines or protocols;
4. explicit criteria for discontinuation of mechanical support and reintubation;
5. identification and control of important co-interventions, including, but not limited to, sedation and general medical care;
6. reporting of clinically relevant outcomes, including duration of mechanical support related to weaning, adverse events and quality of life; and
7. consequences of reintubation for LOS, VAP and mortality.

ACKNOWLEDGEMENTS

We would like to thank the the Cochrane editorial team and our peer reviewers (Dr Harald Herkner, Professor Nathan Pace, Dr Felix Ram, Dr Andrew Jones, Dr Bronagh Blackwood, Dr Eddy Fan and Dr Andrew MacDuff) for their contributions to the review. We would also like to thank the authors of the primary research, who provided additional information pertinent to the design and outcomes of their respective clinical trials, and Dr Sean Keenan, who, although not able to participate in the updated review, provided advice regarding study selection. We thank Haibo Zhang, Haibo Qiu, Wei Ehr Cheng, Zhuxian Feng and Hanpo Yu for their assistance with

translating and contacting authors to clarify publication and study design in earlier issues of this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chen 2001

Methods	Pseudo-randomized (n = 24)
Participants	Participants were admitted with an acute exacerbation of COPD. Participants were invasively ventilated through a nasotracheal tube for 48 to 60 hours Inclusion criteria: pH less than 7.35 PaO_2 less than 45 mm Hg and RR greater than 30 breaths/min
Interventions	Participants were randomly assigned by alternating day of the month to receive noninvasive ventilation in PS mode or continued weaning with invasive PS. PS and PEEP were gradually decreased to facilitate liberation from mechanical support. Ventilation was discontinued after a three-hour SBT was completed and discontinuation criteria were met
Outcomes	1. Mortality 2. VAP 3. Duration of MV related to weaning 4. Hospital LOS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants randomly assigned to group A or B on the basis of order of hospital admission
Allocation concealment (selection bias)	High risk	Used order of hospital admission
Incomplete outcome data (attrition bias) All outcomes	Low risk	None missing
Selective reporting (reporting bias)	Unclear risk	Primary and secondary outcomes not specified. Clinically important outcomes reported

Ferrer 2003

Methods	RCT (n = 43) Two centres Computer-generated list held by investigator not involved in participant care
Participants	Participants with ARF and persistent weaning failure requiring MV for at least 72 hours and failing a two-hour T-piece trial on three consecutive days. Participants were identified by daily screening pre-randomization
Interventions	Participants were randomly assigned to bilevel positive airway pressure in ST mode or invasive weaning with AC or PS. Daily T-piece trials were conducted until extubation in the IPPV group. Periods of SB of increasing duration were used to wean NPPV. IPPV was discontinued after successful completion of a two-hour SBT

Ferrer 2003 *(Continued)*

Outcomes	1. ICU mortality 2. 90-day mortality 3. VAP 4. Duration of MV related to weaning 5. Duration of ETMV 6. Total duration of MV 7. ICU LOS 8. Tracheostomy 9. Reintubation 10. Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomly assigned with the use of a computer-generated table for each centre
Allocation concealment (selection bias)	Low risk	Computer-generated table held by an investigator not involved in the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	None missing
Selective reporting (reporting bias)	High risk	Proportions of weaning successes and failures not reported in publication of full trial. This outcome was previously reported in a smaller number of participants in an earlier abstract publication (2000). Study authors did not continue to collect data on this outcome

Girault 1999

Methods	RCT (n = 33) Opaque envelopes
Participants	Participants with acute-on-chronic respiratory failure (COPD, restrictive, mixed) failing a two-hour T-piece trial after invasive mechanical ventilation for at least 48 hours. Participants were identified through daily screening
Interventions	Participants were randomly assigned to receive invasive pressure support or NPPV delivered in flow or pressure mode. NPPV was delivered intermittently following extubation, separated by periods of SB of increasing duration. Invasive PS was titrated by 3 to 5 cm H_2O according to tolerance. Discontinuation of support followed successful completion of two periods of observation during SB (NPPV) or during PS weaning with optional SBTs (IPPV). Extubation was performed when PS was less than 8 cm H_2O in the IPPV group
Outcomes	1. 90-day mortality 2. Hospital mortality 3. Successful weaning 4. VAP 5. Duration of MV related to weaning 6. Duration of ETMV

Girault 1999 *(Continued)*

	7. Mean daily period of support 8. ICU LOS 9. Hospital LOS 10. Adverse events 11. Reintubation 12. Tracheostomy
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified. Randomization and introduction of the weaning procedure IPSV or NPPV were done during the 24 hours after the two-hour SBT
Allocation concealment (selection bias)	Unclear risk	Opaque envelopes
Incomplete outcome data (attrition bias) All outcomes	Low risk	None missing
Selective reporting (reporting bias)	Low risk	Protocol not available. Published manuscript reports on prespecified outcomes

Girault 2011

Methods	RCT (n = 208) three arms, of which two arms (n = 138) were included in the pooled results 13 ICUs/centres Computer-generated randomization table using variable blocks of four Sealed, opaque envelopes
Participants	Participants with chronic hypercapneic respiratory failure based on history, chest radiograph, arterial blood gases in steady state and/or bicarbonate level and pulmonary function tests (if available) who were intubated for at least 48 hours, regardless of cause of the disorder. Participants were clinically stable for at least 24 hours and underwent an SBT after meeting weaning criteria as determined by a daily screening evaluation. Participants who failed an SBT were assigned to one of the three treatment groups. Two groups (invasive weaning and NPPV weaning) were included in the pooled analysis
Interventions	Participants were randomly assigned to conventional invasive weaning (n = 69), oxygen-therapy (n = 70) or noninvasive ventilation (n = 69). Conventional invasive weaning was performed using one or more daily SBTs with the use of a T-piece or PSV (with or without PEEP) in 20% of participants. In the oxygen-therapy and NPPV groups, respectively, SBTs were followed by a re-ventilation period of at least 30 minutes duration and extubation (same day as randomization) or standard oxygen therapy to maintain $SaO_2 \geq 90\%$ or immediate NPPV with a face mask. NPPV was performed for ≥ six hours and was administered continuously initially and intermittently subsequently with spontaneous breathing periods using supplemental oxygen
Outcomes	1. Mortality (before eighth day after randomization) 2. Mortality (before 29th day after randomization)

Girault 2011 *(Continued)*

	3. ICU mortality (before 29th day after randomization) 4. Hospital mortality (before 29th day after randomization) 5. Total duration of ventilation 6. Duraion of ventilation related to weaning 7. Ventilator-free days 8. Complications (auto extubation, postextubation stridor, tube obstruction, respiratory encephalopathy, bronchial hypersecretion, nosocomial pneumonia, sinusitis, atelectasis, cardiac arrhythmia, haemodynamic collapse, ACPE, paralytic ileus, gastric distension, mask intolerance) 9. Respiratory support at discharge
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization table using variable blocks of four
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes according to centre stratification
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All specific outcomes reported

Hill 2000

Methods	RCT (n = 21) (abstract) Sealed, opaque envelopes
Participants	Participants with acute respiratory failure admitted to a medical intensive care unit and failing a 30-minute T-piece trial were eligible. Participants were identified through daily screening
Interventions	Participants were randomly assigned to receive VPAP using PS, delivered in ST mode, or invasive PS. In both arms, mechanical support was titrated to RR and tidal volume. Whereas two-hour T-piece trials were permitted to discontinue IPPV support in the IPPV group, NPPV was discontinued by gradually increasing periods between NPPV trials until participants were able to breathe spontaneously between NPPV sessions for two hours without increasing RR or dyspnoea
Outcomes	1. Mortality 2. Successful weaning 3. Duration of ETMV 4. Reintubation

Hill 2000 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Clarified to be randomized. Uncertain sequence generation
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes (unclear whether sequentially numbered)
Incomplete outcome data (attrition bias) All outcomes	Low risk	None missing
Selective reporting (reporting bias)	Low risk	Abstract publication only. Published abstract reports the duration of invasive ventilation

Nava 1998a

Methods	RCT (n = 50) Three centres Opaque, sealed envelopes
Participants	Participants admitted with an acute exacerbation of COPD requiring intubation and MV for at least 36 to 48 hours. Relapse was defined as pH less than 7.33, PaO_2 less than 45 mm Hg, severe dyspnoea in the absence of pneumonia or one of 11 nonoperative diagnoses. Participants who met permissive criteria and failed a one-hour T-piece trial were eligible for inclusion
Interventions	Participants were intubated, sedated and paralysed for the first six to eight hours. Those failing a one-hour T-piece trial were randomly assigned to weaning with NPPV or IPPV. NPPV was delivered continuously with at least two periods of SB per day of increasing duration. PS was decreased by 2 to 4 cm H_2O per day in the NPPV group. In the IPPV group, PS was titrated to an RR of less than 25 breaths/min, and twice-daily SBTs were permitted. Discontinuation occurred after successful completion of a three-hour period of SB (NPPV) or SBT (IPPV) and when discontinuation criteria were met
Outcomes	1. 60-day mortality 2. VAP 3. Successful weaning at 60 days 4. Total duration of MV 5. ICU LOS 6. Adverse events 7. Tracheostomy
Notes	

Risk of bias

Nava 1998a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants "were randomly assigned"
Allocation concealment (selection bias)	Low risk	Using sealed, opaque, numbered envelopes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Authors report on important outcomes, including weaning outcomes (success or failure), mortality, VAP, total duration of ventilation and ICU length of stay

Prasad 2009

Methods	
Participants	
Interventions	Participants were initially ventilated in AC mode and were treated with muscle relaxants and sedation to achieve standard ventilator settings. After at least 24 hours of MV and meeting permissive criteria, a T-piece trial was conducted. Participants failing the T-piece trial were randomly assigned to NPPV or IPPV weaning NPPV and IPPV were initiated in pressure mode (with a full face mask) and with the use of invasive PS, respectively. NPPV was applied continuously (except for meals, expectoration). IPAP and EPAP levels were adjusted to achieve satisfactory blood gases and RR less than 25 breaths/min. Thereafter, noninvasive or invasive PS was decreased by 2 cm H_2O every four hours, titrated to good tolerance (monitoring for changes in saturations and RRs). Both noninvasive and invasive PS (above PEEP) were titrated to participant tolerance, blood gases and RR. Once NPPV was decreased to IPAP and EPAP of 8 and 4 cm H_2O, respectively, and invasive PS and PEEP were titrated to 10 and 5 cm H_2O, respectively, with pH greater than or equal to 7.35, SaO_2 greater than or equal to 90%, RR < 30 breaths/min and FiO_2 less than or equal to 40%, participants were allowed to breathe spontaneously on a Venturi mask or were extubated to a Venturi mask
Outcomes	1. 30-day mortality 2. ICU mortality 3. Duration of MV related to weaning 4. ICU LOS 5. VAP 6. Duration of ETMV 7. Deaths due to VAP 8. Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported using a Kendall and Babington table

Prasad 2009 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All specified outcomes reported

Rabie 2004

Methods	RCT (n = 37) One centre (abstract) Allocation concealment not described
Participants	Intubated participants with an acute-on-chronic exacerbation of COPD, who failed a two-hour SBT despite meeting simple weaning criteria
Interventions	After intubation, participants were ventilated in controlled mode, received sedation and paralysis for the first six to eight hours and were treated with PS for an additional 60 hours. A T-piece trial was carried out once participants achieved a satisfactory neurological status and normal temperature and were haemodynamically stable. Participants failing the T-piece trial were randomly assigned to NPPV (initiated by face mask or nasal mask using BiPAP in PAV/T mode) or continued invasive PS. IPPV was titrated by 2 to 4 cm H_2O per day. NPPV was delivered until well tolerated (20 to 22 hours per day), spaced by periods of spontaneous inhalation of oxygen only during meals and for expectoration. The level of PS was decreased by 2 to 4 cm H_2O per day in participants with good tolerance. At least two trials of spontaneous breathing of gradually increasing duration were attempted each day. Criteria for weaning from invasive PS or NPPV were SaO_2 of 90% or greater with an FiO_2 of 40% or less, pH of 7.35 or more, RR less than 35 breaths/min, haemodynamic stability, absence of severe dyspnoea and depressed neurological status. The absence of any of these criteria was considered failure to wean. Participants were screened daily for weaning criteria
Outcomes	1. Weaning failure 2. Weaning duration 3. ICU LOS 4. Hospital LOS 5. Reintubation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Treatment assignment "was randomized". Author confirms that he used a central computer and that group allocation was communicated by a computer
Allocation concealment (selection bias)	Low risk	The author reported that investigators did not know in advance to which arm the participant would be allocated

Rabie 2004 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Personal communication: "Follow-up was complete"
Selective reporting (reporting bias)	Low risk	The authors reported clinically important outcomes. Note is made that they did not report the duration of ventilation related to weaning, although this was not a prespecified outcome in this study

Rabie Agmy 2012

Methods	RCT (n = 264) (abstract) Allocation concealment not described
Participants	Intubated participants with acute-on-chronic respiratory failure due to COPD who failed a two-hour SBT, although they met simple criteria for weaning
Interventions	Conventional invasive PSV (n = 130) was compared with NPPV immediately followed by extubation (n = 134)
Outcomes	1. Gas exchange 2. Duration of ETMV 3. Weaning failure 4. Nosocomial pneumonia 5. ICU LOS 6. Hospital LOS
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization sequence was determined using a central computer, and group allocation was communicated by the computer
Allocation concealment (selection bias)	Low risk	The author reported that investigators did not know in advance to which arm the participant would be allocated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomly assigned participants appear to be accounted for in the analysis
Selective reporting (reporting bias)	Low risk	The authors reported on gas exchange, duration of ETMV, weaning failure rates, nosocomial pneumonia rates and ICU and hospital LOS in their full publication

Tawfeek 2012

Methods	RCT (n = 42) One centre Opaque, sealed, numbered envelopes
Participants	Participants invasively ventilated for longer than 48 hours who failed a two-hour SBT, despite meeting simple weaning criteria
Interventions	Participants who failed an SBT were randomly allocated to SIMV or noninvasive PAV ventilation In the control SIMV group, ventilatory parameters were adjusted until previous $PaCO_2$ and pH values were reached within the first 60 minutes, and the respiratory rate was ≤ 30 breaths/min. In the PAV group, flow and volume assist PAV were adjusted separately
Outcomes	1. Gas exchange 2. Duration of ventilatory support 3. Survival at 30 days 4. Complications: septic shock, pneumothorax and VAP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Low risk	Random assignment was performed using opaque, sealed and numbered envelopes
Incomplete outcome data (attrition bias) All outcomes	Low risk	The authors randomly assigned 42 participants (21 per group), and the denominators for reported outcomes reflect 21 participants per group
Selective reporting (reporting bias)	Low risk	All specified outcomes were reported

Trevisan 2008

Methods	RCT (n = 65) One centre Sealed envelopes
Participants	Participants receiving mechanical ventilation for longer than 48 hours who failed a 30-minute spontaneous breathing trial. Participants considered apt to undergo the weaning procedure were submitted to an SBT. Participants had already been randomly assigned to one of the ventilator modes (NPPV or IPPV) that would be used in the event that they failed an SBT

Trevisan 2008 *(Continued)*

Interventions	After failing a T-piece trial, participants were randomly divided into two groups: Participants were extubated and placed on NPPV or were returned to invasive mechanical ventilation. For participants randomly assigned to NPPV, IPAP was delivered according to participant tolerance (varied from 10 to 30 cm H_2O), and EPAP was set to maintain gas exchange and FiO_2 was set to maintain SpO_2 greater than 90%. A face mask was used. Weaning from NPPV was performed on a daily basis by gradually reducing pressure levels until adequate V_T and minute ventilation levels could be reached and proper alveolar ventilator established. In the IPPV group, a daily SBT was conducted to evaluate the possibility of extubation
Outcomes	1. ICU length of stay 2. Hospital length of stay 3. Total length of stay in hospital 4. ICU mortality 5. Hospital mortality 6. Duration of ventilation after randomization 7. Total duration of mechanical ventilation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors describe the trial as an "experimental randomized clinical trial" and state that a "randomized clinical trial was conducted" but do not provide details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol is not available. The published manuscript includes prespecified outcomes

Vaschetto 2012

Methods	RCT (n = 20) Sealed opaque, sequentially numbered envelopes
Participants	Included participants were mechanically ventilated for longer than 48 hours, had a PaO_2/FiO_2 ratio between 200 and 300 with $FiO_2 \leq 0.60$ in PS mode and total applied pressure (PEEP + inspired pressure) ≤ 25 cm H_2O, $PaCO_2 \leq 50$, pH ≥ 7.35, RR ≤ 30 breaths/min, core temperature < 38.5°C, cough on suctioning, need for tracheobronchial suctioning < two per hour and GCS = 11

Vaschetto 2012 *(Continued)*

Interventions	Participants with hypoxaemic ARF were randomly assigned to early extubation followed by NPPV via helmet (helmet group) or conventional weaning through endotracheal tube (tube group)
Outcomes	1. Days of mechanical ventilation and adherence to study protocol (primary outcomes) 2. Weaning failure 2. Hospital mortality 4. ICU mortality 5. Tracheotomy 6. Continuous sedation 7. Weaning time 8. Septic complications
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors used a table of random numbers, held by investigator not involved in study enrolment
Allocation concealment (selection bias)	Low risk	Participants were randomly assigned with the use of sealed, sequentially numbered, opaque envelopes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All specified outcomes reported

Wang 2004

Methods	RCT (n = 28) One respiratory intensive care unit Allocation concealment not described
Participants	28 invasively ventilated participants with COPD and bronchopulmonary infection. Participants were placed on volume-controlled AC after intubation and then were switched to SIMV + PS + PEEP. When their infection had been brought under control (decreased sputum, sputum less tenacious and purulent, body temperature less than 37.5°C, WBC less than 10×10^9/L, chest x-ray improved but not resolved), participants were treated differently
Interventions	Participants in the IPPV group were ventilated until blood gases approached normal values and they had fulfilled the weaning criteria (spontaneous breathing for longer than three hours, FiO_2 less than or equal to 40%, SpO_2 greater than or equal to 90%, pH greater than or equal to 7.35 and RR less than or equal to 35 breaths/min, with stable haemodynamics and clear consciousness), at which time they

Wang 2004 *(Continued)*

	were extubated. Participants in the NPPV group were extubated and were switched to mask NPPV with PS + PEEP. In both groups, investigators closely monitored the time infection was brought under control, blood gases and mechanical ventilation parameters
Outcomes	1. Time to control of lung infection 2. Length of ICU stay 3. Duration of mechanical ventilation 4. Mortality 5. VAP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported in the abstract that participants were "randomly assigned" and that "28 patients were randomized equally in 2 groups". No mention is made of sequence generation
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	The authors reported clinically important outcomes in the context of wanting to explore the effects of and optimal timing for noninvasive weaning

Wang 2005

Methods	RCT (n = 90) 11 teaching hospitals RICUs, MICUs Allocation concealment not described
Participants	Intubated COPD participants, 85 years of age or younger, with severe hypercapneic respiratory failure due to bronchial pulmonary infection, who were capable of self care in the past year
Interventions	Participants were ventilated with AC (4 to 12 hours) and subsequently with SIMV/PS. Ventiltor rate was gradually decreased to 10 to 12 breaths/min with 10 to 12 cm H_2O PS. When the PIC window appeared, participants were randomly assigned to NPPV (BiPAP) or IPPV (continued SIMV/PS). Nonivasive PS (with PEEP of 4 to 6 cm H_2O) was adjusted to RR < 28 breaths/min, PaO_2 65 to 90 mm Hg and $PaCO_2$ between 45 and 60 mm Hg or at level before extubation. NPPV was considered weaned when PS was decreased until the difference between IPAP and EPAP was less than or equal to 5 cm H_2O and the participant was stable. In the IPPV group, participants were weaned using SIMV + PS. Participants were weaned when the SIMV rate had been decreased to 5 breaths/min, the level of PS was 5 to 7 cm H_2O and the participant had remained stable for four hours
Outcomes	1. Hospital mortality

Wang 2005 *(Continued)*

	2. Total duration of MV 3. ICU LOS 4. Hospital LOS 5. VAP 6. Duration of ETMV 7. Reintubation 8. Costs
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"A prospective randomized controlled trial was conducted in 11 teaching hospitals." Sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data apparent
Selective reporting (reporting bias)	Low risk	The authors wanted to examine the feasibility and efficacy of early extubation with sequential NPPV and reported clinically important outcomes

Zheng 2005

Methods	RCT (n = 33) Allocation concealment not described
Participants	Intubated participants with COPD with severe respiratory failure due to pulmonary infection, who were capable of self care in the past year
Interventions	Once pulmonary infection had been significantly controlled (PIC window appeared), participants were randomly assigned to NPPV versus invasive PS. NPPV was administered in BiPAP mode with a face mask. The criteria for the PIC window were (1) chest x-ray showed improvement in infectious infiltrates, (2) WBC count was less than 10×10^9/L, (3) sputum was decreased and was less purulent or white, with sputum tenacity decreased (lower than grade II). In the IPPV group, participants were weaned with PS. Inspiratory pressure was decreased gradually to less than or equal to 8 cm H_2O to keep RR less than 28 breaths/min, V_T approximately 8 mL/kg, SpO_2 greater than 90% and $PaCO_2$ between 45 and 60 mm Hg or at baseline levels. If participants were stable for four hours with a spontaneous cough, they were extubated. In the NPPV group, participants were ventilated with a nasal or oral mask using BiPAP. Inspiratory pressure and FiO_2 were adjusted to keep RR lower than 28 breaths /min, V_T approximately 8 mL/kg, SpO_2 greater than 90% and $PaCO_2$ between 45 and 60 mm Hg or at pre-extubation levels. All participants received 4 to 6 cm H_2O PEEP to reduce the work of breathing from intrinsic PEEP. The duration of NPPV was longer than two hours initially, and investigators gradually decreased the duration of NPPV and inspiratory pressure daily until NPPV was required for less than two hours per day and inspiratory pressure was less than 10 cm H_2O
Outcomes	1. Hospital mortality 2. Total duration of MV 3. ICU LOS

Zheng 2005 *(Continued)*

	4. Hospital LOS 5. VAP 6. Time to PIC window 7. Duration of ETMV
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Prospective, randomized, controlled clinical study. No mention of sequence generation
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No denominators reported in binary outcomes
Selective reporting (reporting bias)	Low risk	Clinically important outcomes reported

Zou 2006

Methods	RCT (n = 76) RICU (one hospital) Allocation concealment not described
Participants	COPD participants (nasotracheally intubated) with respiratory failure due to pulmonary infection
Interventions	All participants were initially treated with AC + SIMV + PS with 3 to 5 cm H_2O PEEP. After the PIC window (1) full consciousness, effective expectoration, stable haemodynamics, (2) more noticeable absorption of patchy infectious infiltrates compared to before, with no merging shadows and (3) two or more of the following: (a) temperature lower than 38.0°C, (b) peripheral WBC lower than 10.0×10^9/L or percent neutrophils lower than 78.0% and (c) noticeable decrease in the amount of phlegm, the colour of which had turned white or had become lighter and thickness decreased to below grade II) had been reached, participants were randomly assigned to NPPV or IPPV Whereas NPPV was applied with a face or nasal mask in pressure (ST mode), SIMV with PS was used in the IPPV group. IPAP and EPAP were titrated to respiratory condition, arterial gases, RR < 25 to 28 breaths/min, SpO_2 > 90 and $PaCO_2$ between 45 and 60 or at baseline. All participants were kept on noninvasive mechanical ventilation for longer than two hours during the initial application. Noninvasive time was gradually decreased and IPAP was gradually decreased until NPPV was stopped when BiPAP time was less than two hours each day and IPAP level was less than 10 cm H_2O. Invasive PS was gradually reduced to less than or equal to 10 cm H_2O with FiO_2 less than or equal to 50% titrated to the same parameters and to a tidal volume of 8 mL/kg. IPPV was stopped when conditions were stable for longer than four hours and participants were able to swallow and expectorate spontaneously
Outcomes	1. Inpatient mortality 2. Overall MV time 3. ICU LOS 4. Hospital LOS

Zou 2006 *(Continued)*

	5. VAP 6. Duration of ETMV 7. Reintubation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Digital table
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No denominators reported in binary outcomes
Selective reporting (reporting bias)	Low risk	Clinically important outcomes reported

RCT: randomized controlled trial; COPD: chronic obstructive pulmonary disease; b/min: breaths per minute; PaO_2: arterial partial pressure of oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide; RR: respiratory rate; ARF: acute respiratory failure; MV: mechanical ventilation; AC: assist control; PS: pressure support; PAV: proportional assist ventilation; SIMV: synchronized intermittent mandatory ventilation; PEEP: positive end-expiratory pressure; NPPV: noninvasive positive-pressure ventilation; IPPV: invasive positive-pressure ventilation; IPAP: inspiratory positive airway pressure; EPAP: expiratory positive airway pressure; VPAP: ventilator (delivered) positive airway pressure; SB: spontaneous breathing; SBT: spontaneous breathing trial; ST: spontaneous timed; T: timed mode; LOS: length of stay; VAP: ventilator-associated pneumonia; ETMV: endotracheal mechanical ventilation; ICU: intensive care unit; PIC: pulmonary infection control window; RICU: respiratory intensive care unit; MICU: medical intensive care unit; PaO_2: arterial partial pressure of oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide; SpO_2: pulse oximetry oxygen saturation; FiO_2: fractional concentration of inspired oxygen.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Celebi 2008	This study randomly assigned postoperatively 100 participants who had undergone coronary artery bypass surgery to the following four groups: (1) recruitment maneuver (RM) with sustained inflation (n = 25), (2) RM combined with NPPV applied for 30-minute periods every six hours on the first postoperative day after tracheal extubation (n = 25), (3) NPPV after tracheal extubation (n = 25) and (4) a control group that received neither RM or NPPV (n = 25). The authors reported outcomes that included pulmonary function tests, oxygenation index and atelectasis on chest radiograph. This study was excluded because all participants were extubated within six hours of intervention, and because it did not report clinically important outcomes
Du 2009	This trial of 32 elderly participants with ARDS randomly assigned participants to oronasal CPAP or SIMV + PS when the "ARDS control window" appeared. We excluded this trial because it compared extubation versus CPAP with no inspiratory assist. We did not consider CPAP to be a weaning modality
Duan 2012	This randomized trial compared noninvasive weaning (using a face mask) versus continued invasive weaning in 32 exclusively tracheostomized participants. We excluded this trial because (1) tracheostomy was an outcome of our review, (2) this study included a high proportion of participants undergoing prolonged mechanical ventilation and (3) interventions were applied in a different manner in the setting of a tracheostomy. For example, participants randomly assigned to noninvasive weaning could have met criteria to return to invasive ventilation per tracheostomy and subse-

Study	Reason for exclusion
	quently could have been returned to noninvasive ventilation. Similarly, participants randomly assigned to invasive weaning could have undergone a series of SBTs before extubation
Gao Smith 2006	This trial randomly assigned participants who failed a spontaneous breathing trial to standard treatment (placed back on supported breaths) and compared these participants with those who were extubated and placed on noninvasive ventilation. NPPV was initially set at the same support settings as the ventilator and was reduced accordingly by nursing staff. Conventionally ventilated participants underwent daily spontaneous breathing trials. The trial was aborted after approximately eight participants had been enrolled
Ishikawa 1997	This nonrandomized study assessed the role of BIPAP in the management of respiratory failure after cardiovascular surgery. Twenty participants who required respiratory support for longer than 72 hours were studied. BiPAP (n = 8) was compared with unassisted oxygen treatment (n = 12) in the control group. Outcomes reported included respiratory index, alveolar arterial oxygen difference and shunt fraction. This study was excluded as it was not an RCT. In addition, NPPV was not used to facilitate weaning, and physiological end points alone were reported
Jiang 1999	This RCT evaluated the effects of early application of NPPV on extubation outcome in 93 participants after elective (n = 56) or unplanned (n = 37) extubation. After extubation, participants were randomly assigned to receive NPPV or oxygen therapy. This study did not assess the role of NPPV as a weaning modality
Kilic 2008	In this study, 60 participants, after cardiac surgery, were randomly assigned to PS-CPAP or bilevel positive airway pressure, both administered invasively, with bilevel positive airway pressure continued after extubation. Outcomes included blood gases and haemodynamics on arrival to the ICU and one, two, four, six, eight and 12 hours later. This study was excluded, as both treatment groups were predominantly weaned invasively, participants were ventilated for less than 24 hours and the outcomes reported were physiological
Kruger 1998	This RCT evaluated 572 participants who underwent median sternotomy and hypothermic cardiac arrest for cardiopulmonary bypass. Participants were randomly assigned to receive BiPAP (n = 280) or SIMV with PS (n = 292). Outcomes reported included duration of intubation (reported in hours), proportion of participants extubated within six hours, requirement for postoperative analgesia and reintubation rate. This study did not assess the role of NPPV as a weaning strategy in postoperative participants with respiratory failure
Luo 2001	This RCT evaluated 32 participants with COPD requiring intubation for hypercapneic respiratory failure. Participants were randomly assigned to receive BiPAP (n = 19) or conventional therapy (n = 13). Reported outcomes included gas exchange at 45 minutes and 12 hours after extubation and rates of reintubation. This study assessed the role of NPPV not as a weaning strategy, but rather as an aid in transitioning participants to spontaneous breathing. Moreover, in this study, the comparator group was not mechanically ventilated
Matic 2007	This RCT compared NPPV and IPPV as early treatment strategies in COPD participants requiring more than 24 hours of MV. The goals of the study were to compare (1) the influence of physiological parameters on the choice of mechanical ventilation strategy in the treatment of COPD and (2) outcomes using the alternative mechanical ventilation strategies. This study evaluated NPPV and IPPV as initial approaches to mechanical ventilation.
Nava 2011	In this RCT, 82 participants were randomly assigned to receive NPPV plus standard medical therapy or standard medical therapy (SMT). Outcomes included rate of meeting endotracheal intubation (ETI) criteria, mortality rate, respiratory rate, dyspnoea score and arterial blood gases. This study evaluated the role of NPPV in reducing the rate of ETI criteria, not as a weaning strategy
Radojevic 1997	In this prospective, randomized study, participants received BIPAP or PS in the early postoperative period after undergoing aortocoronary bypass surgery (seven hours plus or minus one hour). Criteria for eligibility included an awake participant with neuromuscular activity. The population stud-

Study	Reason for exclusion
	ied represents a cohort of participants in the post–acute care setting that did not require formal weaning
Rong 2012	Participants were not consistently randomly assigned
Rosinha 2002	This prospective RCT allocated participants requiring MV for longer than 72 hours to receive NPPV or supplemental oxygen, by mask, after achieving criteria for extubation. Proportion of successful extubations, length of ICU stay and hospital mortality were reported. This study did not assess the role of NPPV as a weaning strategy, as the comparative group received unassisted oxygen alone
Vargas 2012	This multicentre trial, involving 144 participants, randomly assigned participants to receive NPPV for 48 hours after planned extubation or conventional oxygen treatment. This trial did not assess the role of NPPV in weaning participants from mechanical ventilation, and the comparator group received supplemental oxygen alone
Venkatram 2010	This study was a retrospective study that compared participants managed with NPPV (n = 110) and those managed through invasive mechanical ventilation (n = 156). Duration of ventilatory support, hospital and ICU mortality and NPPV failure rate were reported. The study was not randomized
Wang 2000	This study compared early extubation and sequential NPPV application versus continued invasive ventilation in 11 participants with exacerbations of COPD due to pulmonary infection. The intervention group was compared with a cohort of 11 participants who continuously received invasive MV after control of pulmonary infection had been achieved. This was not an RCT
Wang 2003	This study represents a duplicate publication of Wang 2000
Yang 2009	This study compared standard treatment versus standard treatment with NPPV and did not include invasively ventilated participants
Zheng 2011	This study was a prospective cohort study that included 20 invasively ventilated COPD participants with respiratory failure. Reported outcomes included ventilation and oxygenation index, duration of ETMV, total duration of mechanical ventilation, hospital LOS and rates of reintubation and VAP. This study was excluded, as it was not randomized

BiPAP: bilevel positive airway pressure; RCT: randomized controlled trial; NPPV: noninvasive positive-pressure ventilation; SIMV: synchronized intermittent mandatory ventilation; PS: pressure support; ARF: acute respiratory failure; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease; MV: mechanical ventilation.

Characteristics of ongoing studies *[ordered by study ID]*

Perkins 2013

Trial name or title	Protocolized trial of invasive and noninvasive weaning off ventilation: the BREATHE trial
Methods	RCT (n = 920) http://www.warwick.ac.uk/breathe Allocation concealment not described
Participants	Participants with respiratory failure who received invasive ventilation for longer than 48 hours (from the time of intubation) and who failed a spontaneous breathing test (SBT) Inclusion criteria: 1. Male and female participants, age > 16 years

Perkins 2013 *(Continued)*

	2. Participants with respiratory failure who had received invasive ventilation for longer than 48 hours (from intubation) 3. Failure of an SBT 4. Provision of written informed consent Exclusion criteria: 1. Presence of a tracheostomy 2. Profound neurological deficits 3. Any absolute contraindication to NIV 4. Home ventilation before ICU admission 5. Decision not to reintubate or withdrawal of care 6. Further surgery/procedure requiring sedation planned in the next 48 hours 7. Previous participation in the trial
Interventions	Invasive versus noninvasive weaning Protocolized invasive weaning arm: The participant will be restarted on PS ventilation at the previous settings. The level of PS will be titrated to achieve comfort and RR < 30 breaths/min. Causes for distress/fatigue/weaning failure will be sought and corrective treatments initiated as appropriate. The participant will be reassessed every two hours. If no signs of distress are noted, the level of PS will be reduced by 2 cm H_2O. If at any stage the participant develops distress/fatigue, the PS will be increased by 2 cm H_2O. FiO_2 will be titrated to maintain SaO_2 > 90%. A further SBT will take place each morning. This cycle will continue until the participant has been extubated (passing an SBT or tolerating PS 5 cm H_2O) or a tracheostomy has been performed Protocolized noninvasive weaning arm: Participants will be extubated and immediately provided with NIV with an equivalent level of PS and PEEP to the ventilator settings before extubation. After two hours, if no signs of distress/fatigue are observed, the NIV interface will be removed and the participant will undergo a self-ventilation trial with supplemental oxygen (equivalent to the previous FiO_2) via a standard oxygen mask. If no signs of distress or fatigue develop during the self ventilation trial, the participant will continue to receive unsupported ventilation, with inhaled oxygen provided as required. If the participant subsequently develops signs of distress or fatigue, NIV will be restarted (as below). Otherwise, the participant will continue with unsupported self ventilation. FiO_2 will be titrated to maintain SaO_2 > 90%. If signs of distress or fatigue develop, NIV will be reinstated at the previous settings. The level of PS will be titrated to achieve participant comfort and a RR < 30 breaths/min. Causes for distress/fatigue/weaning failure will be sought and corrective treatments initiated as appropriate. The participant will be reassessed every two hours. If no signs of distress/fatigue are noted, a further trial of self ventilation will be commenced as described above. NIV will be withdrawn when the participant tolerates 12 hours of unsupported spontaneous ventilation In both groups, the active weaning protocol will occur between 8 am and 10 pm. Unless participants develop signs of fatigue or distress, ventilator settings will not be adjusted overnight
Outcomes	Primary: time from randomization to liberation from ventilation Secondary Efficacy: 1. Mortality at 30, 90 and 180 days 2. Duration of invasive mechanical ventilation and total ventilator-free days (invasive and noninvasive ventilation)

Perkins 2013 *(Continued)*

	3. Time to meeting ICU discharge criteria (defined as no further requirement for level 2/3 care) 4. Proportion of participants receiving antibiotics for presumed respiratory infection and total antibiotic days 5. Reintubation rates (protocolized end point and actual events) 6. Tracheostomy Safety 1. Adverse events 2. Serious adverse events Patient-focused outcomes Health-related quality of life, EuroQol, EQ-5D and SF12 at baseline (estimated) and at three and six months
Starting date	1 January 2013
Contact information	Mrs Beverley Hoddell, Clinical Trials Unit, Warwick Medical School, Gibbet Hill Road, Coventry, UK b.hoddell@warwick.ac.uk
Notes	

Smith 2013

Trial name or title	NEXT: Comparison of noninvasive positive pressure ventilation for extubated patients who fail a single spontaneous breathing trial versus conventional weaning
Methods	RCT (n = 8) Stopped early because of the need to fulfil clinical requirements at another hospital
Participants	Inclusion criteria: 1. Participants will have to meet the criteria for reducing breathing support—will not be weaned until physiologically ready 2. Participants will have to be on a breathing machine attached to a tube in the mouth for at least 48 hours (participants who are on a breathing machine for < 48 hours are not seen as difficult to wean from a ventilator) 3. Age > 18 years—participant should be able to make own legal judgements regarding treatment 4. Written informed consent obtained 5. Failed an attempt to try breathing without help Exclusion criteria: 1. Participants are generally not suitable for NIV (grade 3/4 intubation) 2. Gastric/oesophageal surgery on this admission

Smith 2013 *(Continued)*	3. Participants who would not be ready for reintubation once extubated (by investigator decision????)
Interventions	Noninvasive positive-pressure ventilation versus conventional weaning
Outcomes	Primary outcome: duration of time with breathing support tube in the mouth in days Secondary outcomes: length of stay in the intensive care unit and hospital stay in days
Starting date	13 March 2006
Contact information	Dr Fang Gao Department of Anaesthetics, Birmingham Heartlands Hospital, Heart of England NHS Foundation Trust, Bordelsey Green East, Birmingham, UK
Notes	

MV: mechanical ventilation; GCS: Glasgow Coma Scale; PaO_2/FiO_2: ratio of arterial partial pressure of oxygen to fractional concentration of inspired oxygen; PEEP: positive end-expiratory pressure; SBT: spontaneous breathing trial; PS: pressure support; NPPV: noninvasive positive-pressure ventilation; VAP: ventilator-associated pneumonia; ICU: intensive care unit; LOS: length of stay.

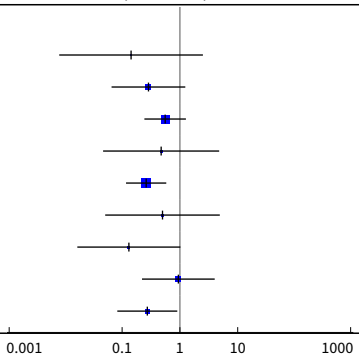
DATA AND ANALYSES

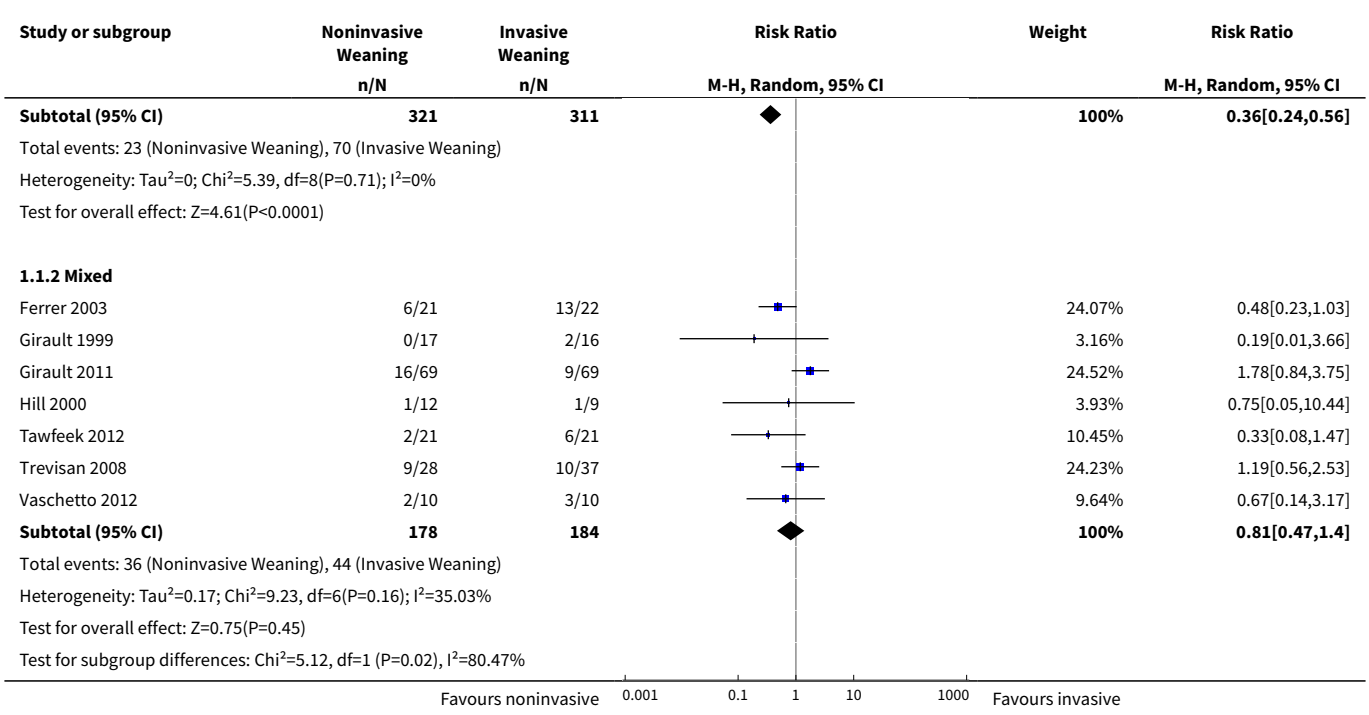
Comparison 1. Noninvasive versus invasive weaning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 COPD	9	632	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.24, 0.56]
1.2 Mixed	7	362	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.47, 1.40]

Analysis 1.1. Comparison 1 Noninvasive versus invasive weaning, Outcome 1 Mortality.

Study or subgroup	Noninvasive Weaning n/N	Invasive Weaning n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 COPD					
Chen 2001	0/12	3/12		2.26%	0.14[0.01,2.5]
Nava 1998a	2/25	7/25		8.55%	0.29[0.07,1.24]
Prasad 2009	5/15	9/15		27.07%	0.56[0.24,1.27]
Rabie 2004	1/19	2/18		3.46%	0.47[0.05,4.78]
Rabie Agmy 2012	7/134	26/130		28.96%	0.26[0.12,0.58]
Wang 2004	1/14	2/14		3.55%	0.5[0.05,4.9]
Wang 2005	1/47	7/43		4.38%	0.13[0.02,1.02]
Zheng 2005	3/17	3/16		8.82%	0.94[0.22,4]
Zou 2006	3/38	11/38		12.95%	0.27[0.08,0.9]

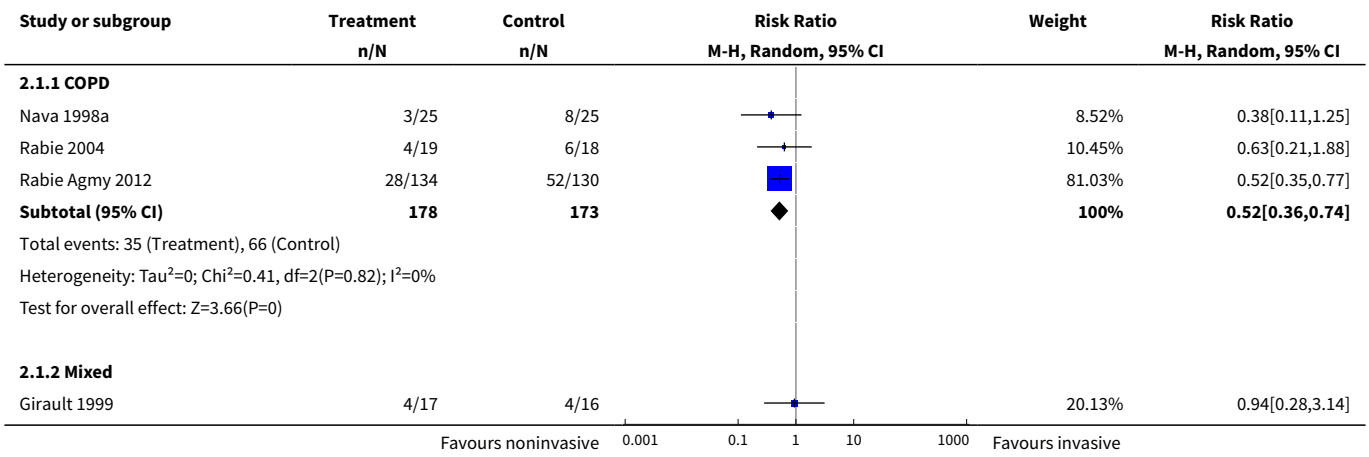


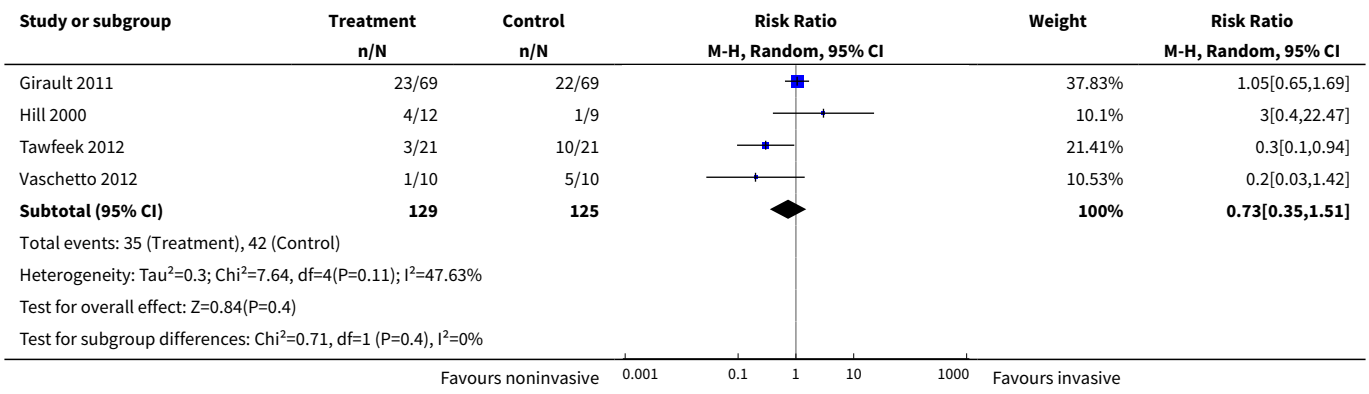


Comparison 2. Noninvasive versus invasive weaning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weaning failure	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 COPD	3	351	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.36, 0.74]
1.2 Mixed	5	254	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.35, 1.51]

Analysis 2.1. Comparison 2 Noninvasive versus invasive weaning, Outcome 1 Weaning failure.

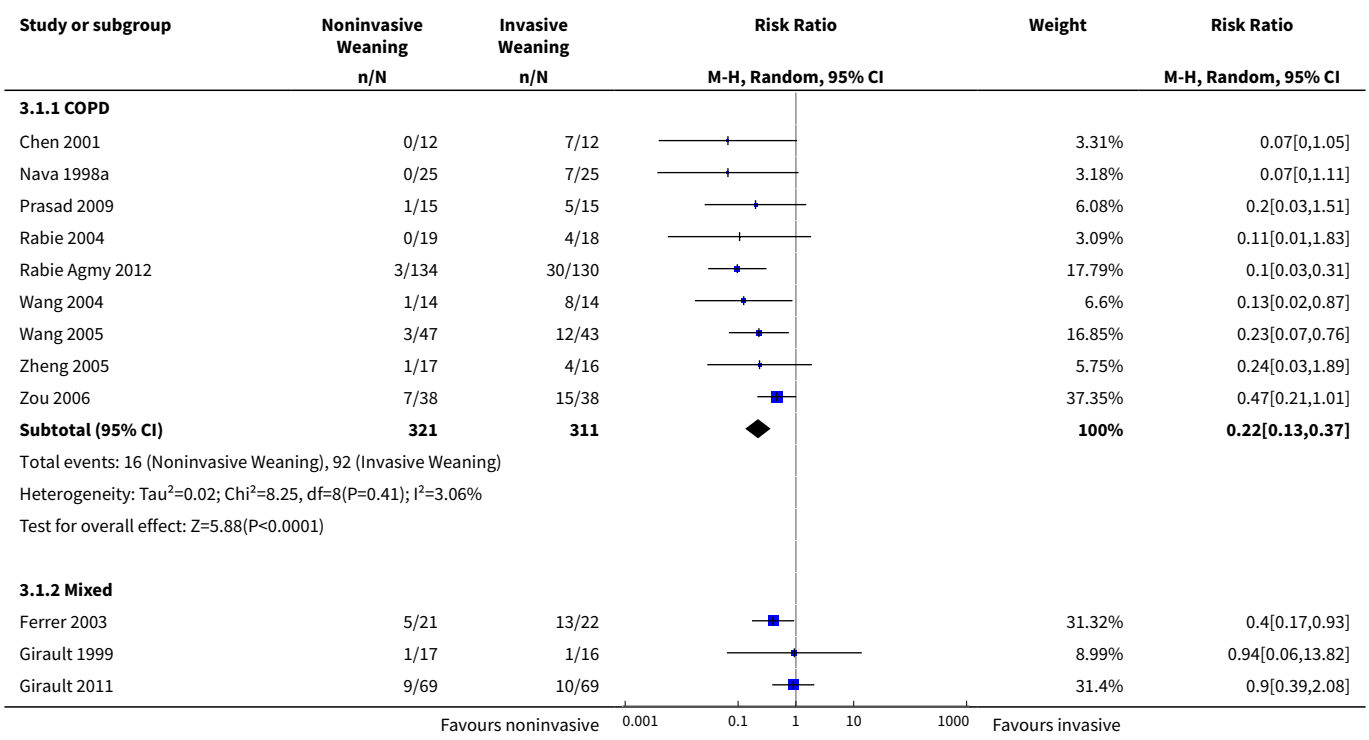


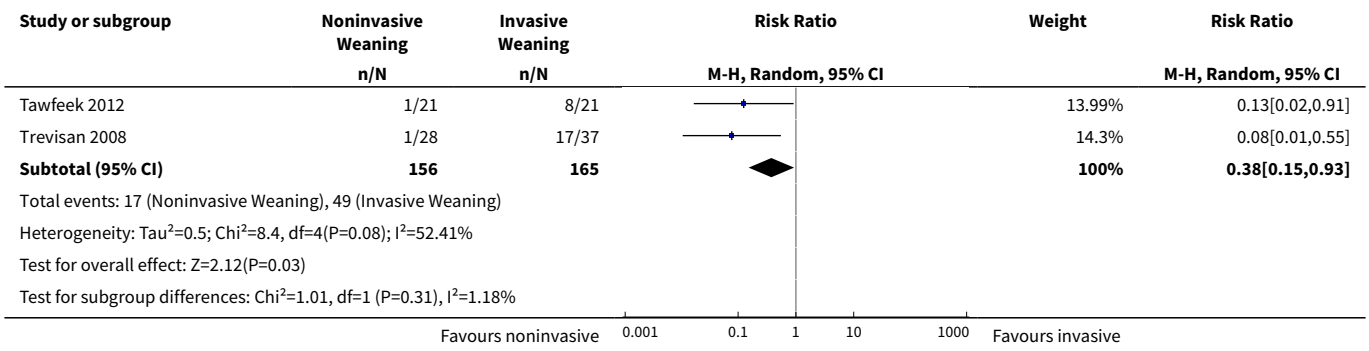


Comparison 3. Noninvasive versus invasive weaning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nosocomial pneumonia	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 COPD	9	632	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.13, 0.37]
1.2 Mixed	5	321	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.15, 0.93]

Analysis 3.1. Comparison 3 Noninvasive versus invasive weaning, Outcome 1 Nosocomial pneumonia.

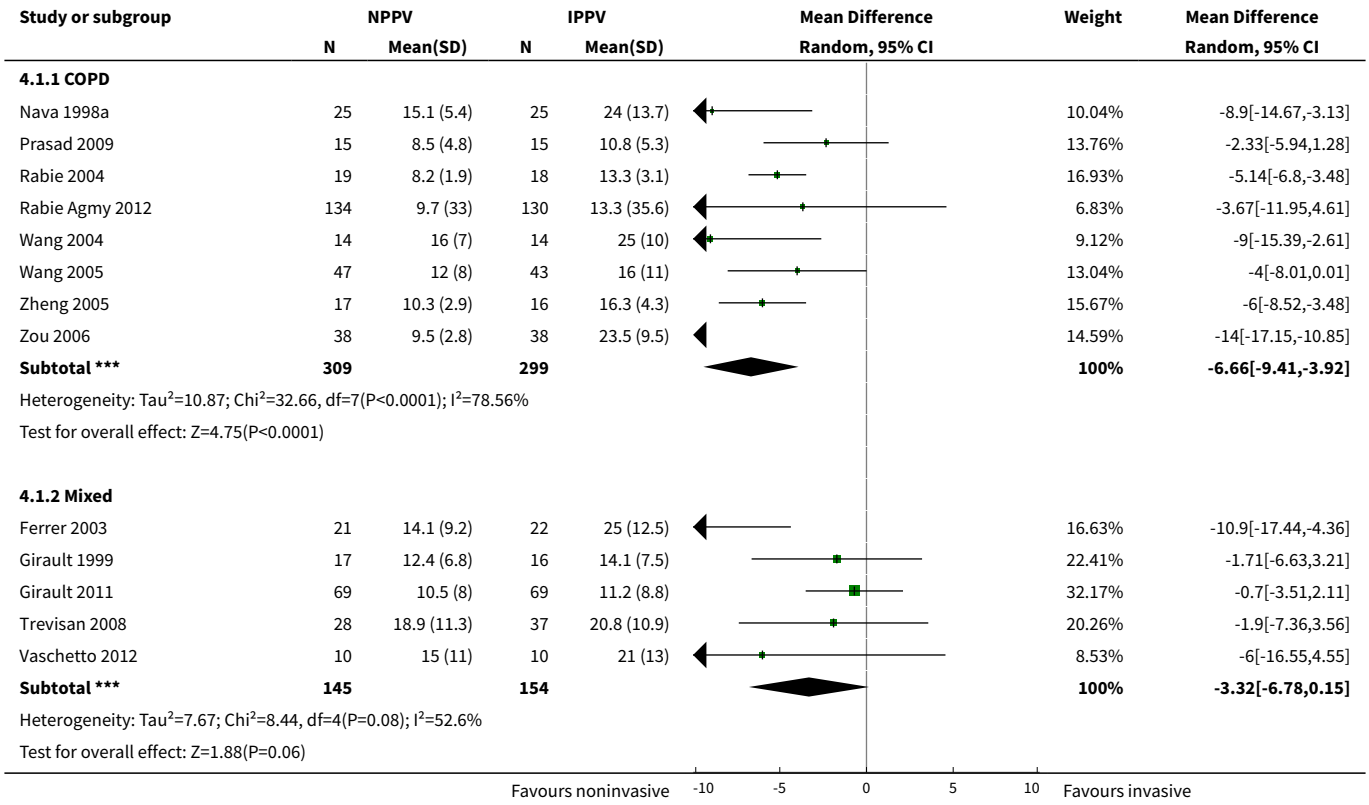


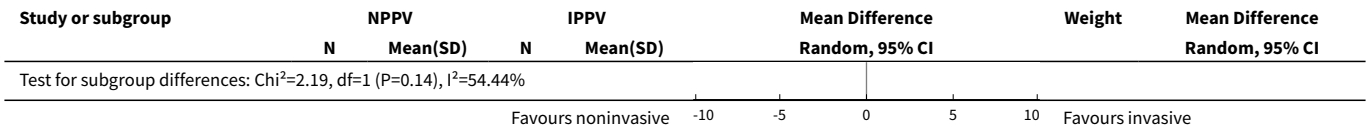


Comparison 4. Noninvasive versus invasive weaning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 LOS ICU	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 COPD	8	608	Mean Difference (IV, Random, 95% CI)	-6.66 [-9.41, -3.92]
1.2 Mixed	5	299	Mean Difference (IV, Random, 95% CI)	-3.32 [-6.78, 0.15]

Analysis 4.1. Comparison 4 Noninvasive versus invasive weaning, Outcome 1 LOS ICU.

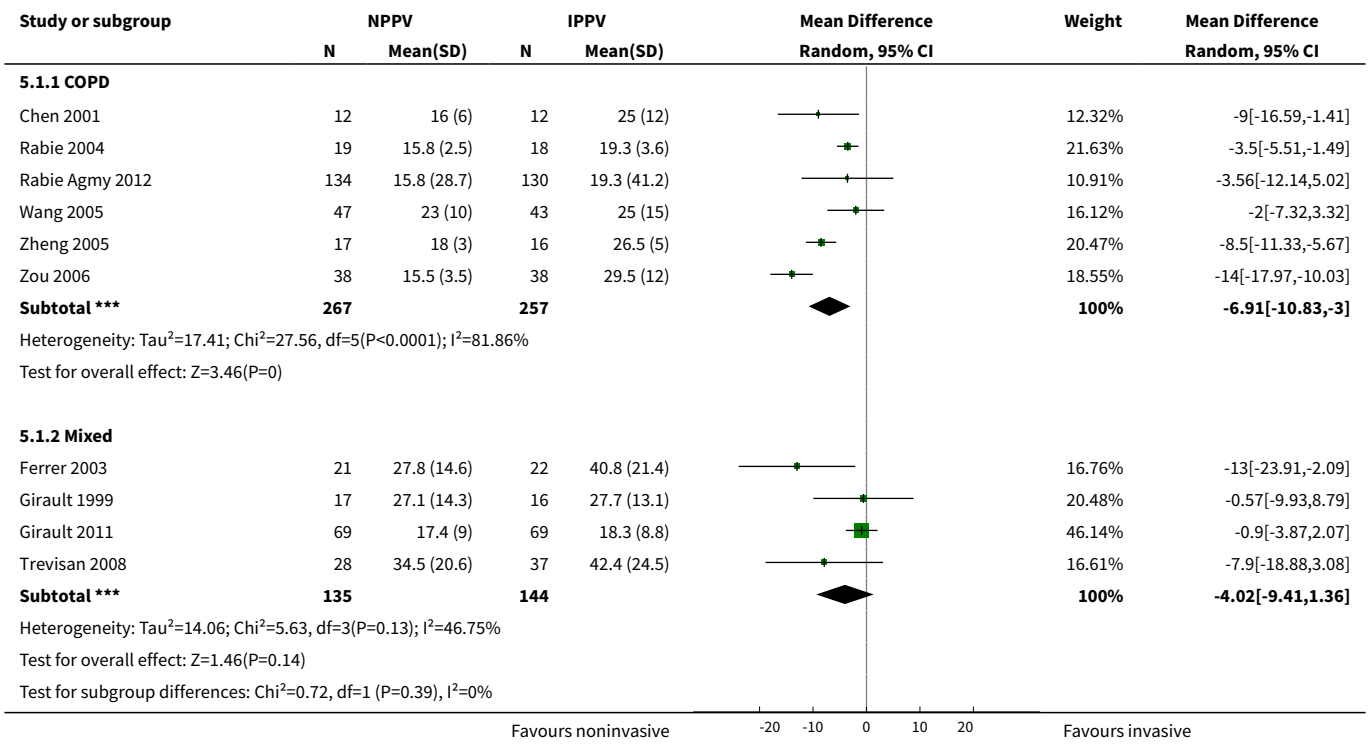




Comparison 5. Noninvasive versus invasive weaning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 LOS hospital	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 COPD	6	524	Mean Difference (IV, Random, 95% CI)	-6.91 [-10.83, -1.00]
1.2 Mixed	4	279	Mean Difference (IV, Random, 95% CI)	-4.02 [-9.41, 1.36]

Analysis 5.1. Comparison 5 Noninvasive versus invasive weaning, Outcome 1 LOS hospital.

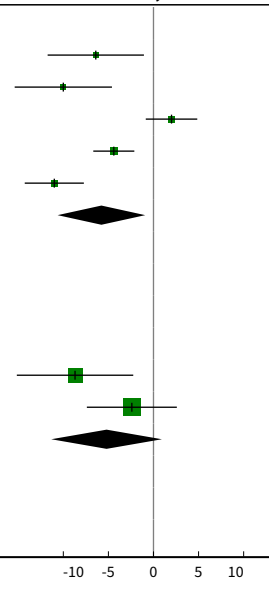


Comparison 6. Noninvasive versus invasive weaning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Average total duration of mechanical ventilatory support	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 COPD	5	277	Mean Difference (IV, Random, 95% CI)	-5.77 [-10.64, -0.91]
1.2 Mixed	2	108	Mean Difference (IV, Random, 95% CI)	-5.20 [-11.34, 0.93]

Analysis 6.1. Comparison 6 Noninvasive versus invasive weaning, Outcome 1 Average total duration of mechanical ventilatory support.

Study or subgroup	NPPV N	NPPV Mean(SD)	IPPV N	IPPV Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.1.1 COPD							
Nava 1998a	25	10.2 (6.8)	25	16.6 (11.8)		18.01%	-6.4[-11.74,-1.06]
Wang 2004	14	11 (5)	14	21 (9)		17.93%	-10[-15.39,-4.61]
Wang 2005	47	13.3 (7.6)	43	11.3 (6.2)		21.32%	2[-0.86,4.86]
Zheng 2005	17	8.4 (2.6)	16	12.8 (3.9)		21.91%	-4.4[-6.68,-2.12]
Zou 2006	38	12.5 (4)	38	23.5 (9.5)		20.83%	-11[-14.28,-7.72]
Subtotal ***	**141**		**136**			**100%**	**-5.77[-10.64,-0.91]**
Heterogeneity: Tau^2=26.72; Chi^2=39.49, df=4(P<0.0001); I^2=89.87%							
Test for overall effect: Z=2.33(P=0.02)							
6.1.2 Mixed							
Ferrer 2003	21	11.4 (8)	22	20.1 (13.1)		44.5%	-8.7[-15.16,-2.24]
Trevisan 2008	28	14.9 (9.9)	37	17.3 (10.5)		55.5%	-2.4[-7.39,2.59]
Subtotal ***	**49**		**59**			**100%**	**-5.2[-11.34,0.93]**
Heterogeneity: Tau^2=11.18; Chi^2=2.29, df=1(P=0.13); I^2=56.34%							
Test for overall effect: Z=1.66(P=0.1)							
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.89), I^2=0%							

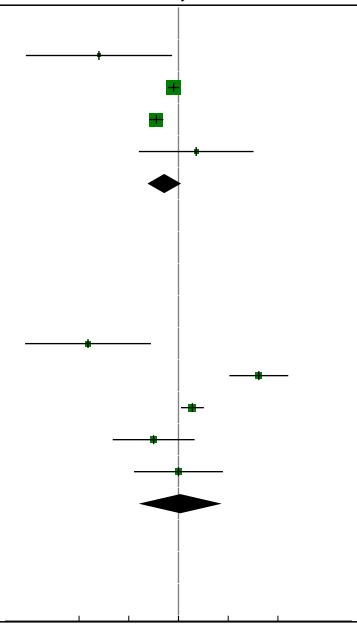


Comparison 7. Noninvasive versus invasive weaning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Average duration of ventilation related to weaning	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 COPD	4	355	Mean Difference (IV, Random, 95% CI)	-1.43 [-3.12, 0.26]
1.2 Mixed	5	290	Mean Difference (IV, Random, 95% CI)	0.17 [-4.01, 4.35]

Analysis 7.1. Comparison 7 Noninvasive versus invasive weaning, Outcome 1 Average duration of ventilation related to weaning.

Study or subgroup	NPPV N	NPPV Mean(SD)	IPPV N	IPPV Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
7.1.1 COPD							
Chen 2001	12	7 (5)	12	15 (12)		4.75%	-8[-15.36,-0.64]
Prasad 2009	15	1.5 (0.7)	15	2 (0.9)		44.54%	-0.49[-1.06,0.08]
Rabie 2004	19	1.6 (1.1)	18	3.8 (1)		43.44%	-2.22[-2.92,-1.52]
Rabie Agmy 2012	134	5.6 (24.5)	130	3.8 (23.3)		7.27%	1.78[-3.99,7.55]
Subtotal ***	**180**		**175**			**100%**	**-1.43[-3.12,0.26]**
Heterogeneity: Tau^2=1.59; Chi^2=18.55, df=3(P=0); I^2=83.83%							
Test for overall effect: Z=1.66(P=0.1)							
7.1.2 Mixed							
Ferrer 2003	21	6.5 (8.2)	22	15.6 (12.6)		15.63%	-9.1[-15.43,-2.77]
Girault 1999	13	11.5 (5.2)	12	3.5 (1.4)		21.7%	8.08[5.12,11.04]
Girault 2011	68	3.6 (4.4)	69	2.2 (2)		23.92%	1.4[0.25,2.55]
Trevisan 2008	28	7.5 (7.8)	37	10 (9.1)		19.7%	-2.5[-6.62,1.62]
Vaschetto 2012	10	4 (4)	10	4 (6)		19.05%	0[-4.47,4.47]
Subtotal ***	**140**		**150**			**100%**	**0.17[-4.01,4.35]**
Heterogeneity: Tau^2=18.67; Chi^2=33.82, df=4(P<0.0001); I^2=88.17%							
Test for overall effect: Z=0.08(P=0.94)							
Test for subgroup differences: Chi^2=0.49, df=1 (P=0.48), I^2=0%							

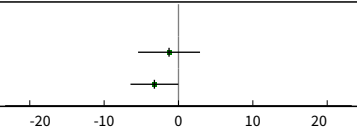


Comparison 8. Noninvasive versus invasive weaning

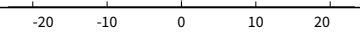
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of endotracheal mechanical ventilation	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 COPD	7	558	Mean Difference (IV, Random, 95% CI)	-7.53 [-11.47, -3.60]
1.2 Mixed	5	159	Mean Difference (IV, Random, 95% CI)	-6.85 [-10.75, -2.95]

Analysis 8.1. Comparison 8 Noninvasive versus invasive weaning, Outcome 1 Duration of endotracheal mechanical ventilation.

Study or subgroup	NPPV N	NPPV Mean(SD)	IPPV N	IPPV Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
8.1.1 COPD							
Prasad 2009	15	6.2 (5.2)	15	7.5 (6.4)		13.51%	-1.27[-5.44,2.9]
Rabie 2004	19	4.8 (3.8)	18	8 (5.9)		14.39%	-3.24[-6.45,-0.03]



Study or subgroup	NPPV N	NPPV Mean(SD)	IPPV N	IPPV Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Rabie Agmy 2012	134	4.8 (10.1)	130	8 (15.7)		14.4%	-3.24[-6.44,-0.04]
Wang 2004	14	4.8 (0.8)	14	21 (9)		12.94%	-16.2[-20.93,-11.47]
Wang 2005	47	6.4 (4.4)	43	11.3 (6.2)		15.13%	-4.9[-7.14,-2.66]
Zheng 2005	17	4.4 (2.5)	16	12.8 (3.9)		15.13%	-8.4[-10.65,-6.15]
Zou 2006	38	7.5 (1.9)	38	23.5 (9.5)		14.5%	-16[-19.08,-12.92]
Subtotal * **	**284**		**274**			**100%**	**-7.53[-11.47,-3.6]**
Heterogeneity: Tau²=25.34; Chi²=69.9, df=6(P<0.0001); I²=91.42%							
Test for overall effect: Z=3.75(P=0)							
8.1.2 Mixed							
Ferrer 2003	21	9.5 (8.3)	22	20.1 (13.1)		19.61%	-10.6[-17.12,-4.08]
Girault 1999	17	4.6 (1.9)	16	7.7 (3.8)		38.73%	-3.13[-5.18,-1.08]
Hill 2000	12	6.6 (6.9)	9	15.2 (21)		6.38%	-8.6[-22.87,5.67]
Tawfeek 2012	21	12.8 (8.3)	21	22.3 (13.3)		19.03%	-9.5[-16.21,-2.79]
Vaschetto 2012	10	7.6 (6)	10	15 (10.8)		16.25%	-7.4[-15.06,0.26]
Subtotal * **	**81**		**78**			**100%**	**-6.85[-10.75,-2.95]**
Heterogeneity: Tau²=9.14; Chi²=8.07, df=4(P=0.09); I²=50.43%							
Test for overall effect: Z=3.44(P=0)							
Test for subgroup differences: Chi²=0.06, df=1 (P=0.81), I²=0%							



Favours noninvasive — Favours invasive

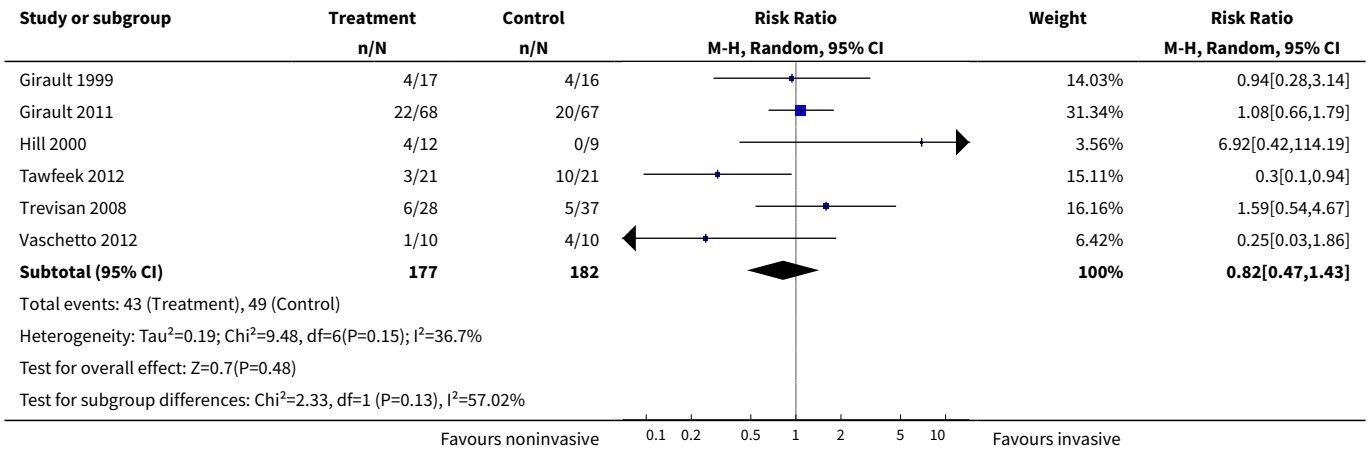
Comparison 9. Noninvasive versus invasive weaning

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Reintubation	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 COPD	3	430	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.35, 0.70]
1.2 Mixed	7	359	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.47, 1.43]

Analysis 9.1. Comparison 9 Noninvasive versus invasive weaning, Outcome 1 Reintubation.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
9.1.1 COPD					
Rabie Agmy 2012	28/134	52/130		77.05%	0.52[0.35,0.77]
Wang 2005	4/47	8/43		9.28%	0.46[0.15,1.41]
Zou 2006	5/38	13/38		13.67%	0.38[0.15,0.97]
Subtotal (95% CI)	**219**	**211**		**100%**	**0.49[0.35,0.7]**
Total events: 37 (Treatment), 73 (Control)					
Heterogeneity: Tau²=0; Chi²=0.38, df=2(P=0.83); I²=0%					
Test for overall effect: Z=4.02(P<0.0001)					
9.1.2 Mixed					
Ferrer 2003	3/21	6/22		13.37%	0.52[0.15,1.83]

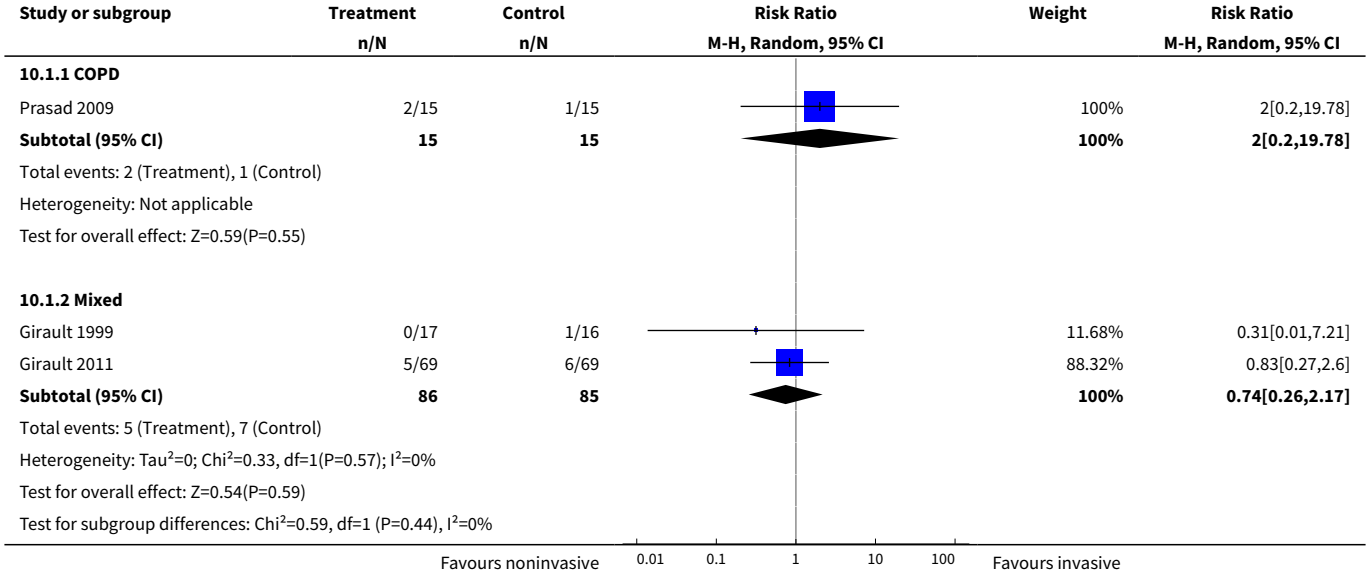
Favours noninvasive — Favours invasive



Comparison 10. Noninvasive versus invasive weaning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Arrhythmia	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 COPD	1	30	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.20, 19.78]
1.2 Mixed	2	171	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.26, 2.17]

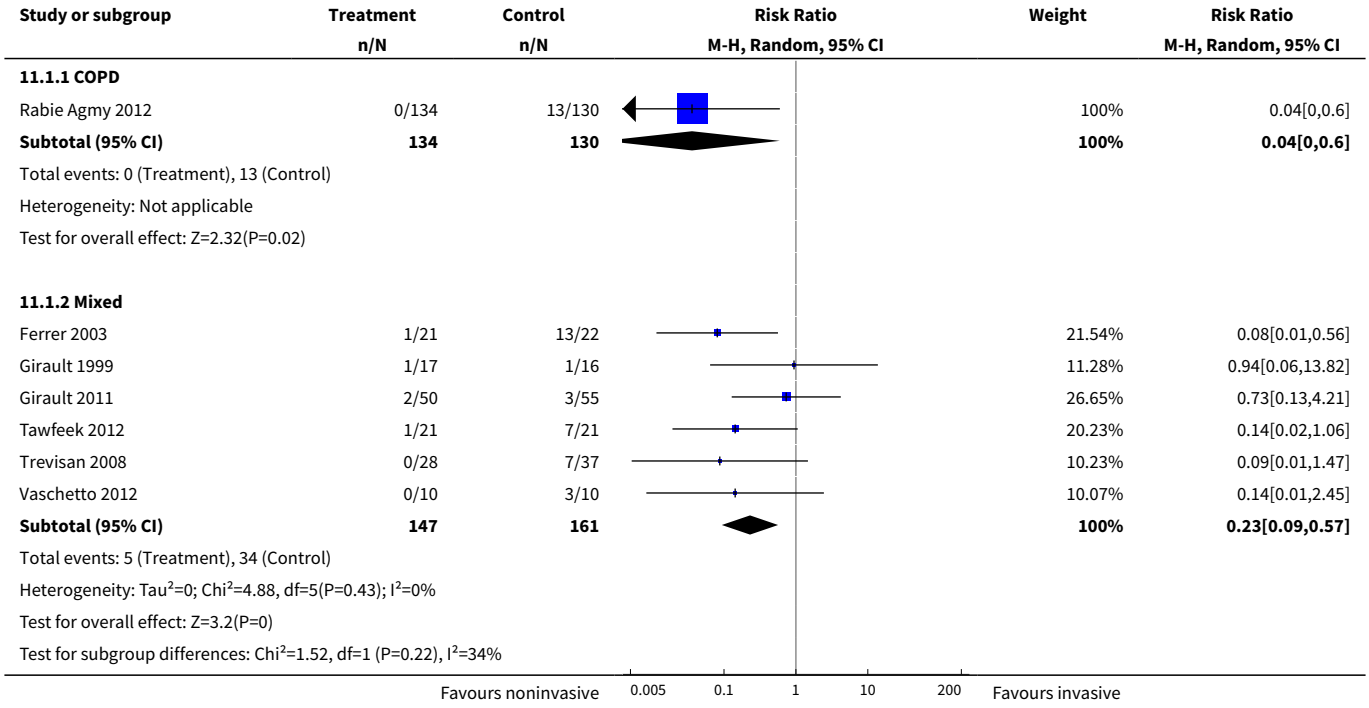
Analysis 10.1. Comparison 10 Noninvasive versus invasive weaning, Outcome 1 Arrhythmia.



Comparison 11. Noninvasive versus invasive weaning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tracheostomy	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 COPD	1	264	Risk Ratio (M-H, Random, 95% CI)	0.04 [0.00, 0.60]
1.2 Mixed	6	308	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.09, 0.57]

Analysis 11.1. Comparison 11 Noninvasive versus invasive weaning, Outcome 1 Tracheostomy.

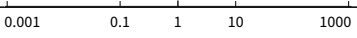


Comparison 12. Sensitivity analysis: noninvasive versus invasive weaning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality excluding quasi-randomized trial	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Nosocomial pneumonia excluding quasi-randomized trial	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

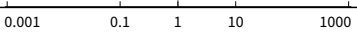
Analysis 12.1. Comparison 12 Sensitivity analysis: noninvasive versus invasive weaning, Outcome 1 Mortality excluding quasi-randomized trial.

Study or subgroup	NPPV n/N	IPPV n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ferrer 2003	6/21	13/22		0%	0.48[0.23,1.03]
Girault 1999	0/17	2/16		0%	0.19[0.01,3.66]
Girault 2011	16/69	9/69		0%	1.78[0.84,3.75]
Hill 2000	1/12	1/9		0%	0.75[0.05,10.44]
Nava 1998a	2/25	7/25		0%	0.29[0.07,1.24]
Prasad 2009	5/15	9/15		0%	0.56[0.24,1.27]
Rabie 2004	1/19	2/18		0%	0.47[0.05,4.78]
Rabie Agmy 2012	7/134	26/130		0%	0.26[0.12,0.58]
Tawfeek 2012	5/21	4/21		0%	1.25[0.39,4.02]
Trevisan 2008	9/28	10/37		0%	1.19[0.56,2.53]
Vaschetto 2012	2/10	3/10		0%	0.67[0.14,3.17]
Wang 2004	1/14	2/14		0%	0.5[0.05,4.9]
Wang 2005	1/47	7/43		0%	0.13[0.02,1.02]
Zheng 2005	3/17	3/16		0%	0.94[0.22,4]
Zou 2006	3/38	11/38		0%	0.27[0.08,0.9]



Analysis 12.2. Comparison 12 Sensitivity analysis: noninvasive versus invasive weaning, Outcome 2 Nosocomial pneumonia excluding quasi-randomized trial.

Study or subgroup	NPPV n/N	IPPV n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ferrer 2003	5/21	13/22		0%	0.4[0.17,0.93]
Girault 1999	1/17	1/16		0%	0.94[0.06,13.82]
Girault 2011	9/69	10/69		0%	0.9[0.39,2.08]
Nava 1998a	0/25	7/25		0%	0.07[0,1.11]
Prasad 2009	1/15	5/15		0%	0.2[0.03,1.51]
Rabie 2004	0/19	4/18		0%	0.11[0.01,1.83]
Rabie Agmy 2012	3/134	30/130		0%	0.1[0.03,0.31]
Tawfeek 2012	1/21	8/21		0%	0.13[0.02,0.91]
Trevisan 2008	1/28	17/37		0%	0.08[0.01,0.55]
Wang 2004	1/14	8/14		0%	0.13[0.02,0.87]
Wang 2005	3/47	12/43		0%	0.23[0.07,0.76]
Zheng 2005	1/17	4/16		0%	0.24[0.03,1.89]
Zou 2006	7/38	15/38		0%	0.47[0.21,1.01]



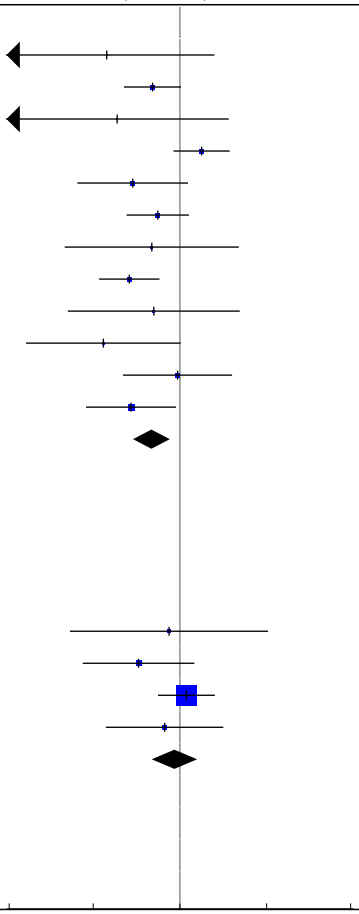
Comparison 13. Noninvasive versus invasive weaning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality greater than or equal to 50% COPD versus less than 50% COPD	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Greater than or equal to 50% COPD	12	846	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.29, 0.76]
1.2 Less than 50% COPD	4	148	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.47, 1.58]

Analysis 13.1. Comparison 13 Noninvasive versus invasive weaning, Outcome 1 Mortality greater than or equal to 50% COPD versus less than 50% COPD.

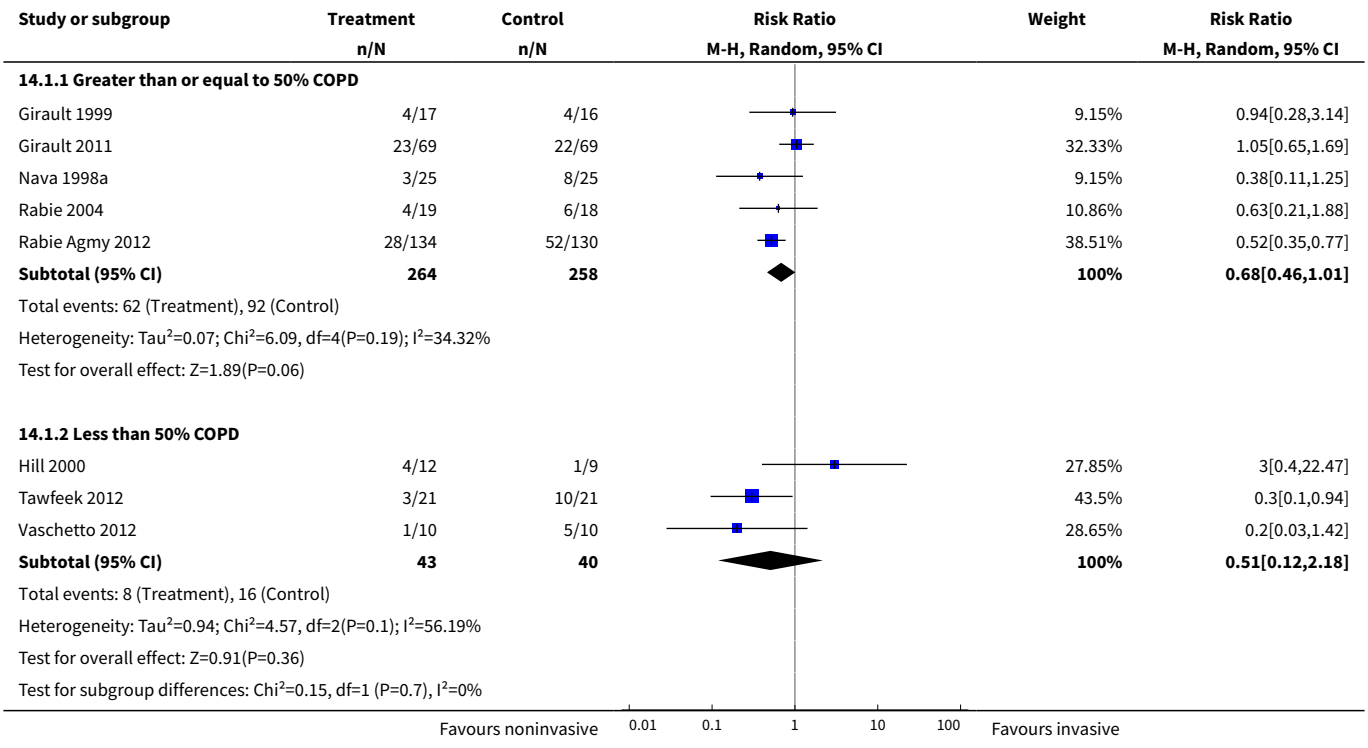
Study or subgroup	NPPV n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
13.1.1 Greater than or equal to 50% COPD					
Chen 2001	0/12	3/12		2.59%	0.14[0.01,2.5]
Ferrer 2003	6/21	13/22		14.82%	0.48[0.23,1.03]
Girault 1999	0/17	2/16		2.43%	0.19[0.01,3.66]
Girault 2011	16/69	9/69		15.03%	1.78[0.84,3.75]
Nava 1998a	2/25	7/25		7.47%	0.29[0.07,1.24]
Prasad 2009	5/15	9/15		13.92%	0.56[0.24,1.27]
Rabie 2004	1/19	2/18		3.74%	0.47[0.05,4.78]
Rabie Agmy 2012	7/134	26/130		14.29%	0.26[0.12,0.58]
Wang 2004	1/14	2/14		3.82%	0.5[0.05,4.9]
Wang 2005	1/47	7/43		4.55%	0.13[0.02,1.02]
Zheng 2005	3/17	3/16		7.63%	0.94[0.22,4]
Zou 2006	3/38	11/38		9.7%	0.27[0.08,0.9]
Subtotal (95% CI)	**428**	**418**		**100%**	**0.47[0.29,0.76]**
Total events: 45 (NPPV), 94 (Control)					
Heterogeneity: Tau^2=0.27; Chi^2=18.99, df=11(P=0.06); I^2=42.07%					
Test for overall effect: Z=3.04(P=0)					
13.1.2 Less than 50% COPD					
Hill 2000	1/12	1/9		5.21%	0.75[0.05,10.44]
Tawfeek 2012	2/21	6/21		16.47%	0.33[0.08,1.47]
Trevisan 2008	9/28	10/37		63.45%	1.19[0.56,2.53]
Vaschetto 2012	2/10	3/10		14.86%	0.67[0.14,3.17]
Subtotal (95% CI)	**71**	**77**		**100%**	**0.86[0.47,1.58]**
Total events: 14 (NPPV), 20 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.45, df=3(P=0.49); I^2=0%					
Test for overall effect: Z=0.48(P=0.63)					
Test for subgroup differences: Chi^2=2.39, df=1 (P=0.12), I^2=58.1%					



Comparison 14. Noninvasive versus invasive weaning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weaning failure greater than or equal to 50% COPD	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Greater than or equal to 50% COPD	5	522	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.46, 1.01]
1.2 Less than 50% COPD	3	83	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.12, 2.18]

Analysis 14.1. Comparison 14 Noninvasive versus invasive weaning, Outcome 1 Weaning failure greater than or equal to 50% COPD.



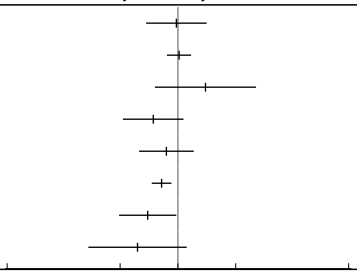
Comparison 15. Noninvasive versus invasive weaning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weaning failure	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Nosocomial pneumonia	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Average duration of ventilation related to weaning	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
4 Reintubation	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

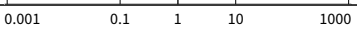
Analysis 15.1. Comparison 15 Noninvasive versus invasive weaning, Outcome 1 Weaning failure.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Girault 1999	4/17	4/16		0%	0.94[0.28,3.14]
Girault 2011	23/69	22/69		0%	1.05[0.65,1.69]
Hill 2000	4/12	1/9		0%	3[0.4,22.47]
Nava 1998a	3/25	8/25		0%	0.38[0.11,1.25]
Rabie 2004	4/19	6/18		0%	0.63[0.21,1.88]
Rabie Agmy 2012	28/134	52/130		0%	0.52[0.35,0.77]
Tawfeek 2012	3/21	10/21		0%	0.3[0.1,0.94]
Vaschetto 2012	1/10	5/10		0%	0.2[0.03,1.42]



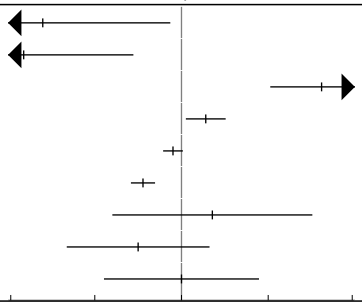
Analysis 15.2. Comparison 15 Noninvasive versus invasive weaning, Outcome 2 Nosocomial pneumonia.

Study or subgroup	Noninvasive Weaning n/N	Invasive Weaning n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2001	0/12	7/12		0%	0.07[0,1.05]
Ferrer 2003	5/21	13/22		0%	0.4[0.17,0.93]
Girault 1999	1/17	1/16		0%	0.94[0.06,13.82]
Girault 2011	9/69	10/69		0%	0.9[0.39,2.08]
Nava 1998a	0/25	7/25		0%	0.07[0,1.11]
Prasad 2009	1/15	5/15		0%	0.2[0.03,1.51]
Rabie 2004	0/19	4/18		0%	0.11[0.01,1.83]
Rabie Agmy 2012	3/134	30/130		0%	0.1[0.03,0.31]
Tawfeek 2012	1/21	8/21		0%	0.13[0.02,0.91]
Trevisan 2008	1/28	17/37		0%	0.08[0.01,0.55]
Wang 2004	1/14	8/14		0%	0.13[0.02,0.87]
Wang 2005	3/47	12/43		0%	0.23[0.07,0.76]
Zheng 2005	1/17	4/16		0%	0.24[0.03,1.89]
Zou 2006	7/38	15/38		0%	0.47[0.21,1.01]



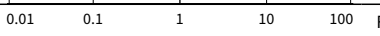
Analysis 15.3. Comparison 15 Noninvasive versus invasive weaning, Outcome 3 Average duration of ventilation related to weaning.

Study or subgroup	NPPV N	NPPV Mean(SD)	IPPV N	IPPV Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Chen 2001	12	7 (5)	12	15 (12)		0%	-8[-15.36,-0.64]
Ferrer 2003	21	6.5 (8.2)	22	15.6 (12.6)		0%	-9.1[-15.43,-2.77]
Girault 1999	13	11.5 (5.2)	12	3.5 (1.4)		0%	8.08[5.12,11.04]
Girault 2011	68	3.6 (4.4)	69	2.2 (2)		0%	1.4[0.25,2.55]
Prasad 2009	15	1.5 (0.7)	15	2 (0.9)		0%	-0.49[-1.06,0.08]
Rabie 2004	19	1.6 (1.1)	18	3.8 (1)		0%	-2.22[-2.92,-1.52]
Rabie Agmy 2012	134	5.6 (24.5)	130	3.8 (23.3)		0%	1.78[-3.99,7.55]
Trevisan 2008	28	7.5 (7.8)	37	10 (9.1)		0%	-2.5[-6.62,1.62]
Vaschetto 2012	10	4 (4)	10	4 (6)		0%	0[-4.47,4.47]



Analysis 15.4. Comparison 15 Noninvasive versus invasive weaning, Outcome 4 Reintubation.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ferrer 2003	3/21	6/22		0%	0.52[0.15,1.83]
Girault 1999	4/17	4/16		0%	0.94[0.28,3.14]
Girault 2011	22/68	20/67		0%	1.08[0.66,1.79]
Hill 2000	4/12	0/9		0%	6.92[0.42,114.19]
Rabie Agmy 2012	28/134	52/130		0%	0.52[0.35,0.77]
Tawfeek 2012	3/21	10/21		0%	0.3[0.1,0.94]
Trevisan 2008	6/28	5/37		0%	1.59[0.54,4.67]
Vaschetto 2012	1/10	4/10		0%	0.25[0.03,1.86]
Wang 2005	4/47	8/43		0%	0.46[0.15,1.41]
Zou 2006	5/38	13/38		0%	0.38[0.15,0.97]



ADDITIONAL TABLES

Table 1. Populations and interventions in studies of noninvasive ventilation in critically ill adults

Study	No of participants	Inclusion criteria (participants)	Inclusion criteria (weaning eligibility)	Experimental strategy	Control strategy
Nava 1998	50	Exacerbation of COPD. Intubated for at least 36 to 48 hours	Simple weaning criteria, 1-hour SBT failure	Noninvasive pressure support on conventional ventilator delivered with face mask	Invasive PS
Girault 1999	33	Acute-on-chronic respiratory failure (COPD, restrictive, or mixed populations). Intubated for at least 48 hours	Simple weaning criteria, 2-hour SBT failure	Flow or pressure mode with nasal or face mask	Flow or pressure mode (PS)

Table 1. Populations and interventions in studies of noninvasive ventilation in critically ill adults *(Continued)*

Hill 2000	21	Acute respiratory failure	30-minute SBT failure	NPPV using VPAP in ST-A mode	Invasive PS
Chen 2001	24	Exacerbation of COPD. Intubated for at least 48 to 60 hours. Saturation ≥ 88% on FiO_2 of 40%	Day 3+ weaning criteria	Bilevel NPPV (pressure mode)	Invasive PS
Ferrer 2003	43	Acute respiratory failure and persistent weaning failure. Intubated for at least 72 hours	Two-hour SBT failure on 3 consecutive days	Bilevel NPPV in ST mode delivered with face or nasal mask	AC or invasive PS
Rabie Agmy 2004	37	Exacerbation of COPD	Two-hour SBT failure	NPPV (proportional assist in timed mode) delivered by face or nasal mask	Invasive PS
Wang 2004	28	COPD. Bronchopulmonary infection	PIC window	NPPV (pressure mode) delivered by mask (unspecified)	SIMV + PS
Zheng 2005	33	COPD. Severe pulmonary infection	PIC window	Bilevel NPPV (pressure mode) delivered by face or nasal mask	Invasive PS
Zou 2006	76	COPD with severe respiratory failure. Pulmonary infection	PIC window	Bilevel NPPV (pressure, ST mode) delivered by nasal or oronasal mask	SIMV + PS
Wang 2005	90	COPD with severe hypercapneic respiratory failure. Pneumonia or purulent bronchitis. Age ≤ 85. Capable of self care in past year	PIC window	Bilevel NPPV (pressure mode)	SIMV + PS
Trevisan 2008	65	Invasively ventilated > 48 hours	30-minute SBT failure	Bilevel NPPV (pressure mode) delivered by face mask	Invasive mechanical ventilation
Prasad 2009	30	COPD. Hypercapneic respiratory failure	Two-hour SBT failure	Bilevel NPPV (pressure mode) delivered by full face mask	Invasive PS
Girault 2011	138	Chronic hypercapneic respiratory failure invasively ventilated for at least 48 hours	Two-hour SBT failure	Noninvasive PS ± PEEP or bilevel NIV with face mask (initial choice)	Invasive PS with once-daily SBT with T-piece or PS ± PEEP
Rabie Agmy 2012	264	Acute-on-chronic exacerbation of COPD	Two-hour SBT failure	NPPV (pressure, ST mode)	Invasive PS

Table 1. Populations and interventions in studies of noninvasive ventilation in critically ill adults *(Continued)*

Tawfeek 2012	42	Invasively ventilated for > 48 hours	Two-hour SBT failure	Noninvasive PAV ventilation delivered by face mask	SIMV
Vaschetto 2012	20	Hypoxemic respiratory failure invasively ventilated for at least 48 hours	PS with PEEP + inspiratory support, ≤ 25 cm H_2O PEEP 8 to 13 cm H_2O PaO_2/FiO_2 200 to 300 mm Hg with $FiO_2 \leq 0.6$	Helmet NPPV	Invasive PS with SBT when P/F ratio > 250 mm Hg

COPD = chronic obstructive pulmonary disease; NPPV = noninvasive positive-pressure ventilation; PS = pressure support; PEEP = positive end-expiratory pressure; PIC = pulmonary infection control window; ST = spontaneous timed; AC = assist control; SIMV = synchronized intermittent mandatory ventilation; P/F ratio = ratio of arterial concentration of oxygen to fractional concentration of oxygen administered; SBT = spontaneous breathing trial; PAV = proportional assist ventilation.

APPENDICES

Appendix 1. Search strategy for CENTRAL, *The Cochrane Library*

#1 MeSH descriptor Positive-Pressure Respiration explode all trees
#2 post-extubation or postextubation
#3 MeSH descriptor Ventilator Weaning explode all trees
#4 #1 OR #2 OR #3
#5 MeSH descriptor Respiratory Insufficiency explode all trees
#6 MeSH descriptor Postoperative Complications, this term only
#7 #5 OR #6
#8 #4 and #7

Appendix 2. Search strategy for MEDLINE (Ovid SP)

1. exp POSITIVE-PRESSURE RESPIRATION/ or exp VENTILATOR WEANING/ or post?extubation.mp.
2. POSTOPERATIVE CARE/ or exp RESPIRATORY INSUFFICIENCY/ or POSTOPERATIVE COMPLICATIONS
3. (randomised controlled trial.pt. or controlled clinical trial.pt.or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals.sh not (humans.sh and animals.sh))
4. 1 and 2 and 3

Appendix 3. Search strategy for EMBASE (Ovid SP)

1. exp positive-end-expiratory-pressure/ or exp artificial-ventilation/ or post?extubation*.mp.
2. postoperative-care/ or exp respiratory-failure/
3. ((RANDOMIZED-CONTROLLED-TRIAL/ or RANDOMIZATION/ or CONTROLLED-STUDY/ or MULTICENTER-STUDY/ or PHASE-3-CLINICAL-TRIAL/ or PHASE-4-CLINICAL-TRIAL/ or DOUBLE-BLIND-PROCEDURE/ or SINGLE-BLIND-PROCEDURE/) or ((RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*) or ((SINGL* or DOUBL* or TREBL* or TRIPL*) adj3 (BLIND* or MASK*))).ti,ab) not (animals.sh not (humans.sh and animals.sh))
4. 1 and 2 and 3

WHAT'S NEW

Date	Event	Description
13 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

HISTORY

Protocol first published: Issue 2, 2003
Review first published: Issue 4, 2003

Date	Event	Description
4 December 2013	New search has been performed	Included trials: We included four new trials (Girault 2011; Rabie Agmy 2012; Tawfeek 2012; Vaschetto 2012) in this updated review. For one trial with three arms, we included two arms relevant to our research question (Girault 2011). Quality assessment: In this update, we evaluated and recorded the presence of true randomization and the use of concealed allocation to minimize selection bias. Additionally, we evaluated reports of randomized trials for completeness of outcome data and selective outcomes reported to assess for attrition and reporting biases, respectively. Unlike in the previous review (Burns 2010), we did not include in our quality assessment the use of daily screening to identify participants capable of unassisted breathing; predefined, permissive weaning criteria to identify weaning candidates (including but not limited to minute ventilation, tidal volume (V_T), vital capacity, respiratory rate, rapid shallow breathing index, Glasgow Coma Scale, presence of spontaneous ventilatory efforts and a cough reflex, requirement for positive end-expiratory pressure (PEEP) and ability to maintain arterial oxygen saturation above 90% on a fractional concentration of inspired oxygen (FiO_2) of less than 0.50) and performace of spontaneous breathing trials (SBTs). We did not include assessment of the use of weaning protocols or guidelines (in both groups) and criteria for failure of a prerandomization SBT, discontinuation of mechanical ventilation (in both groups) and extubation, reintubation due to poor reporting of these aspects of trial design and implementation and concerns over the reliability of efforts to acquire these details amidst language issues. We contacted authors to ask them to describe specific features of their trials including use of daily screening and a prerandomization SBT; however, we did not include these items in the quality assessment in this update. Exclusion criteria: We updated our exclusion criteria to exclude studies evaluating exclusively tracheostomized participants as (1) tracheostomy was an outcome of this review, (2) these studies typically include a high proportion of participants undergoing prolonged mechanical ventilation and (3) application of the interventions could be different in the setting of a tracheostomy (e.g. participants randomly assigned to noninvasive weaning may meet criteria to return to invasive ventilation per tracheostomy and subsequent-

Date	Event	Description
		ly be returned to noninvasive ventilation. Similarly, participants randomly assigned to invasive weaning may undergo a series of spontaneous breathing trials (SBTs) before extubation). Summary of findings: We included in this update SoF tables for the outcomes of mortality, weaning failure, ventilator-associated pneumonia (VAP) and reintubation .
4 December 2013	New citation required but conclusions have not changed	A new author, Azra Premji, joined the review team in June 2012.
6 July 2010	New citation required but conclusions have not changed	We invited one new review author (Sean Keenan) to participate in the update to the previously published meta-analysis (Burns 2003). 1. Study assessment and outcomes reporting, methodology assessment: in assessing methodologic quality, we assessed whether trials included discontinuation OR extubation criteria in both treatment arms in order to limit performance bias as trials infrequently reported extubation criteria as part of the weaning strategy separate from initial extubation criteria. 2. In this update, we were able to pool three adverse events (reintubation, tracheostomy and arrhythmias) reported in a small number of studies. 3. New findings: despite identification of new evidence, our conclusion remains unchanged. Similar to our previous findings, compared to invasive weaning, we found that noninvasive weaning significantly decreased mortality, ventilator associated pneumonia, intensive care unit and hospital length of stay, the total duration of ventilation and duration of endotracheal mechanical ventilation. Noninvasive weaning had no effect on weaning failures or the duration of ventilation related to weaning; no study reported on quality of life. Excluding a single quasi-randomised trial maintained the significant reduction in mortality and ventilator associated pneumonia. Subgroup analyses suggested that the benefits on mortality and weaning failures were non significantly greater in trials enrolling exclusively chronic obstructive pulmonary disease patients versus mixed populations.
6 July 2010	New search has been performed	We reran our searches from July 2003 to April 2008. We included seven new RCTs (Prasad 2008; Rabie 2004; Trevisan 2008; Wang 2004; Wang 2005; Zheng 2005; Zou 2006) in this version. Our previous version (Burns 2003) included five RCTS. This new updated version includes 12 RCTs, involving 530 patients in total. Of those 12 RCTs, eight trials included patients with chronic obstructive pulmonary disease and four trials included mixed populations. We identified and excluded three new trials (Matic 2007; Wang 2000; Wang 2003) in this version. One study (Girault 2002) is now completed and awaiting publication.
17 February 2009	Amended	Converted to new review format
8 July 2004	New search has been performed	We revised the variance for the duration of ETMV reported in the abstract publication from standard error of the mean to stan-

Date	Event	Description
		dard deviation. The summary estimate of effect changed slightly from a WMD of -6.60 days (95% CI, -11.70 to -1.87) to a WMD of -6.32 days (95% CI, -12.12 to -0.52). The test for overall effect and the test for heterogeneity remained statistically significant. We revised the variance for the duration of ETMV reported in the abstract publication from standard error of the mean to standard deviation. The summary estimate of effect changed slightly from a WMD of -6.60 days (95% CI, -11.70 to -1.87) to a WMD of -6.32 days (95% CI, -12.12 to -0.52). The test for overall effect and the test for heterogeneity remained statistically significant. In addition, we tested the difference in relative risk (RR) between sub-categories (COPD versus mixed populations) using a z-test in the subgroup analyses section of the 'Results'. We considered a P-value less than or equal to 0.05 to be statistically significant. We revised the number of patients in the computation of the WMD for the duration of mechanical ventilation related to weaning in the study by Girault et al (Girault 1999) to reflect that this outcome was reported in successful patients. The summary estimate of effect changed minimally from a WMD -2.71 (95% CI, -15.71 to 10.29, P = 0.68) to a WMD of -2.72 days (95% CI, -15.58 to 10.14, P = 0.68).

CONTRIBUTIONS OF AUTHORS

Karen Burns (KB): proposed the research question and title; designed the protocol; reviewed and retrieved relevant articles; assessed methodologic quality of retrieved articles; abstracted data as the primary review author; entered data; conducted the statistical analysis and prepared the final review.

Neill Adhikari (NA): reviewed and retrieved relevant articles; assessed methodologic quality of retrieved articles; abstracted data as the second review author and revised the final review for important intellectual content.

Azra Premji (AP): assisted in retrieving articles and updating the text of the review. Also revised the final review for methodologic quality and scientific integrity.

Maureen Meade (MM): adjudicated disagreements; supervised the methodologic integrity of the review; reviewed the manuscript for methodologic and scientific integrity.

DECLARATIONS OF INTEREST

Karen EA Burns: none known.

Maureen O Meade: Dr Meade has received in-kind support from industry in the form of equipment loans for use in the context of a multicentre clinical trial.

Azra Premji: none known.

Neill KJ Adhikari: none known.

SOURCES OF SUPPORT

Internal sources

- New source of support, Other.

External sources

- Dr Burns is the recipient of a Canadian Institutes of Health Research Clinician Scientist Phase 2 Award, Canada.

NOTES

In the previously published protocol, as part of an a priori sensitivity analysis, we stated that we would assess the impact of the cause of respiratory failure (COPD vs non-COPD) on (1) the proportion of weaning failures and (2) mortality. In the last version of this review, we identified two studies restricted to participants with COPD and three studies with mixed participant populations. In the absence of individual participant data, we compared studies restricted to COPD participants versus those with mixed participant populations. To explore for potential differences in response to NPPV, we compared studies enrolling at least 50% COPD participants versus those enrolling less than 50% COPD participants, in terms of mortality.

To search EMBASE, we used the following Emtree terms: respiratory failure (explode), positive end-expiratory pressure (explode) and weaning (explode). In addition, we used the Emtag: artificial ventilation.

In the protocol, we stated that the MEDLINE search strategy would be limited to include the following publication types: clinical trials, controlled clinical trials, randomized controlled trials, multicenter studies and meta-analyses. In the review, we did not limit the most recent literature search by publication type.

October 2013

Quality assessment

In this update, we evaluated and recorded the presence of true randomization and use of concealed allocation to minimize selection bias. Additionally, we evaluated reports of randomized trials for completeness of outcome data and selective outcomes reporting to assess for attrition and reporting biases, respectively.

Unlike in the previous review (Burns 2010), we did not include in our quality assessment the use of daily screening to identify participants capable of unassisted breathing; inclusion of predefined, permissive weaning criteria to identify weaning candidates (including but not limited to minute ventilation, tidal volume (V_T), vital capacity, respiratory rate, rapid shallow breathing index, Glasgow Coma Scale, presence of spontaneous ventilatory efforts and a cough reflex, requirement for PEEP and ability to maintain arterial oxygen saturation above 90% on a fractional concentration of inspired oxygen (FiO_2) of less than 0.50) and performance of spontaneous breathing trials (SBTs). We did not include assessment of the use of weaning protocols or guidelines (in both groups) and criteria for failure of prerandomization SBT, discontinuation of mechanical ventilation (in both groups) and extubation, reintubation due to poor reporting of these aspects of trial design and implementation and concerns over the reliability of efforts to acquire these details amidst language issues. We contacted study authors to ask them to describe specific features of their trials, including use of daily screening and a prerandomization SBT; however, we did not include them in the quality assessment in this update.

Summary of findings

We included in this update SoF tables for the outcomes of mortality, weaning failure, VAP and reintubation.

Exclusion criteria

We updated our exclusion criteria to exclude studies evaluating exclusively tracheostomized participants, as (1) tracheostomy was an outcome of this review, (2) these studies typically include a high proportion of participants undergoing prolonged mechanical ventilation and (3) application of the interventions could be different in the setting of a tracheostomy (e.g. participants randomly assigned to noninvasive weaning may meet criteria to return to invasive ventilation per tracheostomy and subsequently may be returned to noninvasive ventilation. Similarly, participants randomly assigned to invasive weaning may undergo a series of SBTs before extubation).

INDEX TERMS

Medical Subject Headings (MeSH)

Noninvasive Ventilation [*methods]; Pneumonia, Ventilator-Associated [prevention & control]; Positive-Pressure Respiration [*methods] [mortality]; Pulmonary Disease, Chronic Obstructive [mortality] [*therapy]; Quality of Life; Randomized Controlled Trials as Topic; Respiratory Insufficiency [mortality] [*therapy]; Ventilator Weaning [*methods]

MeSH check words

Adult; Humans