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Early versus late tracheostomy for critically ill patients (Review)

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[Intervention Review]

Early versus late tracheostomy for critically ill patients

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ABSTRACT

Background

Long-term mechanical ventilation is the most common situation for which tracheostomy is indicated for patients in intensive care units (ICUs). 'Early' and 'late' tracheostomies are two categories of the timing of tracheostomy. Evidence on the advantages attributed to early versus late tracheostomy is somewhat conflicting but includes shorter hospital stays and lower mortality rates.

Objectives

To evaluate the effectiveness and safety of early (≤ 10 days after tracheal intubation) versus late tracheostomy (> 10 days after tracheal intubation) in critically ill adults predicted to be on prolonged mechanical ventilation with different clinical conditions.

Search methods

This is an update of a review last published in 2012 (Issue 3, *The Cochrane Library*) with previous searches run in December 2010. In this version, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 8); MEDLINE (via PubMed) (1966 to August 2013); EMBASE (via Ovid) (1974 to August 2013); LILACS (1986 to August 2013); PEDro (Physiotherapy Evidence Database) at www.pedro.fhs.usyd.edu.au (1999 to August 2013) and CINAHL (1982 to August 2013). We reran the search in October 2014 and will deal with any studies of interest when we update the review.

Selection criteria

We included all randomized and quasi-randomized controlled trials (RCTs or QRCTs) comparing early tracheostomy (two to 10 days after intubation) against late tracheostomy (> 10 days after intubation) for critically ill adult patients expected to be on prolonged mechanical ventilation.

Data collection and analysis

Two review authors extracted data and conducted a quality assessment. Meta-analyses with random-effects models were conducted for mortality, time spent on mechanical ventilation and time spent in the ICU.

Main results

We included eight RCTs (N = 1977 participants). At the longest follow-up time available in these studies, evidence of moderate quality from seven RCTs (n = 1903) showed lower mortality rates in the early as compared with the late tracheostomy group (risk ratio (RR) 0.83, 95% confidence interval (CI) 0.70 to 0.98; P value 0.03; number needed to treat for an additional beneficial outcome (NNTB) ≅ 11). Divergent

results were reported on the time spent on mechanical ventilation and no differences were noted for pneumonia, but the probability of discharge from the ICU was higher at day 28 in the early tracheostomy group (RR 1.29, 95% CI 1.08 to 1.55; P value 0.006; NNTB ≅ 8).

Authors' conclusions

The whole findings of this systematic review are no more than suggestive of the superiority of early over late tracheostomy because no information of high quality is available for specific subgroups with particular characteristics.

PLAIN LANGUAGE SUMMARY

Timing of tracheostomy for critically ill patients who are predicted to be on long-term artificial respiration

Review question: We reviewed available evidence on the effects of early tracheostomy (≤ 10 days after tracheal intubation) as compared with late tracheostomy (> 10 days after tracheal intubation) in terms of mortality in critically ill patients who predicted to be on long-term artificial respiration.

Background: Tracheostomy is a surgical procedure in which an external artificial opening is made in the trachea (windpipe). Long-term mechanical ventilation (whereby a machine is used to mechanically assist breathing) is the most common situation for which tracheostomy is indicated for patients in intensive care units (ICUs). 'Early' and 'late' tracheostomies may be undertaken.

Study characteristics: The evidence is current to August 2013. We included eight studies with a total of 1977 patients allocated to either early or late tracheostomy. Four studies received financial support from different institutions that did not participate in the study or in preparing the content of the final publications. We reran the search in October 2014. We will deal with any studies of interest when we update the review.

Key results: Patients receiving early tracheostomy had lower risk of mortality at the longest follow-up time available in seven studies that measured mortality (ranging from 28 days to two years of follow-up), as compared with patients subjected to a late tracheostomy. However, the available evidence should be considered with caution because information is insufficient regarding any subgroup(s) or individual characteristic(s) potentially associated with the best indications for early or late tracheostomy. According to available results, approximately 11 patients would need to be treated with an early instead of a late tracheostomy to prevent one death. Results concerning the time spent on mechanical ventilation are not definitive, but they suggest benefits associated with early tracheostomy. Two studies show a significantly higher probability of discharge from the ICU at 28 days of follow-up in the early tracheostomy group and no significant differences for pneumonia. Possible differences between early and late tracheostomy have yet to be adequately investigated in high-quality studies because no information is available on the best indication for either early or late tracheostomy in patients with specific characteristics.

Quality of the evidence: The quality of the evidence varied according to which outcome was analysed. Evidence was considered of moderate quality for mortality and time spent on mechanical ventilation; of high quality for discharge from the ICU at day 28; and of very low and low quality for pneumonia and sternal wound infection, respectively. Clinical and methodological heterogeneities between studies were the main factors responsible for downgrading the quality of available evidence.

Summary of findings for the main comparison. Early vs late tracheostomy for critically ill patients

Early vs late tracheostomy for critically ill patients

Patient or population: critically ill patients
Settings: intensive care unit
Intervention: early vs late tracheostomy

Outcomes	Illustrative comparative risks[a] (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Early vs late tracheostomy				
Mortality at longest follow-up time available in the studies Follow-up: 28 days to 2 years	**Study population**		**RR 0.83** (0.7 to 0.98)	1903 (7 studies)	⊕⊕⊕⊖ **Moderate**[b,c,d,e,f,g,h,i]	
	532 per 1000	**442 per 1000** (372 to 521)				
	Moderate					
	537 per 1000	**446 per 1000** (376 to 526)				
Ventilator-free days during 1 to 28 days Follow-up: 28 days		Mean ventilator-free days during 1 to 28 days in the intervention groups was **1.62 higher** (0.01 lower to 3.25 higher)		335 (2 studies)	⊕⊕⊕⊖ **Moderate**[b,d,f,g,h,i,j,k]	
Days of MV during 1 to 60 days Follow-up: 60 days	See comment	See comment	Not estimable	336 (2 studies)	⊕⊖⊖⊖ **Very low**[b,d,f,g,h,l,m.n]	
Length of ICU stay Follow-up: mean ICU stay days	See comment	See comment	Not estimable	336 (2 studies[14])	⊕⊖⊖⊖ **Very low**[b,d,f,g,h,k,o,p]	
ICU discharge (at day 28 after randomization) Follow-up: 28 days	**Study population**		**RR 1.29** (1.08 to 1.55)	538 (2 studies)	⊕⊕⊕⊕ **High**[b,d,e,f,g,h,i,j]	
	410 per 1000	**528 per 1000**				

		(442 to 635)			
	Moderate				
	433 per 1000	**559 per 1000** (468 to 671)			
Pneumonia	See comment	See comment	Not estimable	948 (5 studies)	⊕⊖⊖⊖ **Very low**[b,d,f,g,h,i,q,r]

[a]The basis for the **assumed risk** (e.g. 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.

See 'Risk of bias' table found in the Characteristics of included studies table and in Figure 1 and Figure 2.
Inconsistency test between studies may represent moderate statistical heterogeneity, but individual estimate effects in 59 out of all 87 outcomes analysed (67.8%) had the same direction, which favoured the early tracheostomy group. Clinical heterogeneity is a condition that is naturally present among critically ill patients.
All studies compared early versus late tracheostomy for critically ill patients.
Statistical analysis resulted in a relatively short confidence interval and P value < 0.05.
There is no reason to suspect publication bias.
RR between 0.5 and 2.0 = not large effect, according to Grade Working Group criteria.
Grade Working Group recommends to not rate the influence of all plausible residual confounding factors and to choose no in randomized trials downgraded for any reason.
Grade Working Group recommends to not rate the presence of dose-response gradient and to choose no in randomized trials downgraded for any reason.
Inconsistency test (I^2) = 0%.
Statistical analysis resulted in a relatively large confidence interval and P value > 0.05.
Inconsistency test (I^2) = 92% may represent considerable heterogeneity, but the intervention is associated with benefit in all other outcomes.
Statistical analysis resulted in a very large confidence interval and P value > 0.05.
Substantial variation between studies, from 1.4 days to 9.8 days.
Inconsistency test (I^2) = 91% may represent considerable heterogeneity.
Substantial variation between studies, from 1.6 mean days to 11.6 mean days.
Inconsistency test (I^2) = 71% may represent substantial heterogeneity.
[r]Statistical analysis resulted in a relatively short confidence interval, but P value > 0.05.

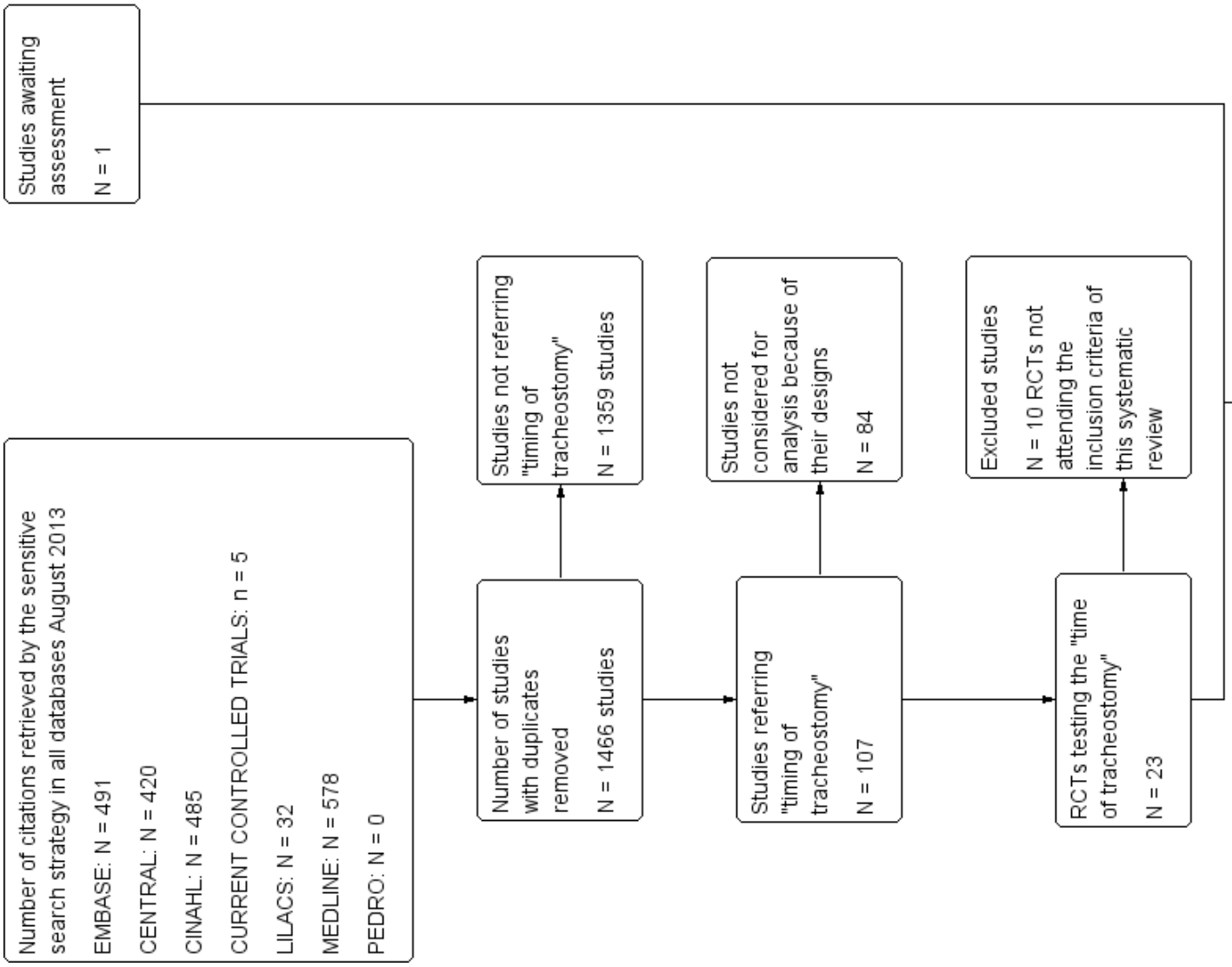


Figure 1. Flow diagram of studies from studies recovered by the sensitive search strategy for inclusion in the systematic review.

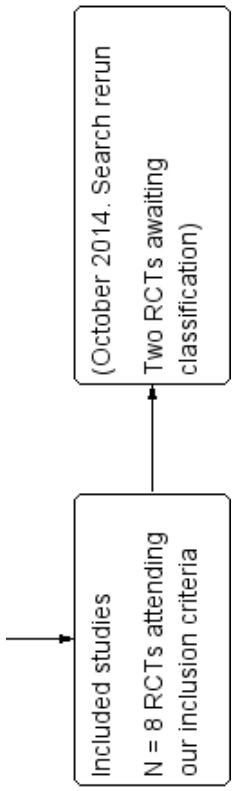


Figure 1. (Continued)

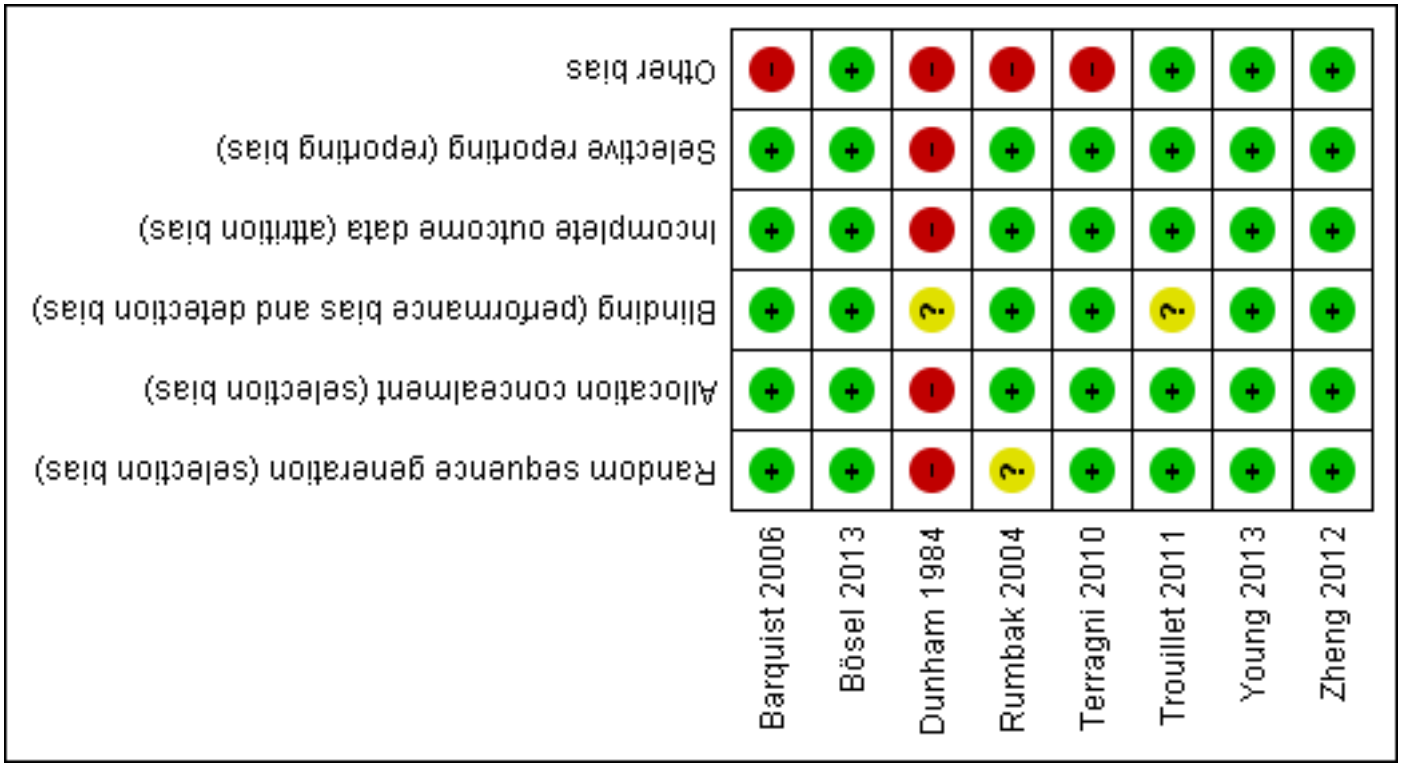


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

BACKGROUND

Description of the condition

Long-term mechanical ventilation is the most common situation for which tracheostomy is indicated for patients in intensive care units (ICUs) (Heffner 2001). Although the definition of prolonged ventilation can include periods as short as 24 hours (Criner 1994; Griffiths 2005), only patients who are foreseen to be on artificial ventilation for approximately 10 days or longer (Armstrong 1998; Plummer 1989) are generally subjected to elective tracheostomy. In this circumstance, tracheostomy is offered as a strategy to reduce respiratory injury and other undesired consequences of prolonged translaryngeal intubation. These include ventilator-associated pneumonia (Ranes 2006), sinusitis (Holzapfel 1993) and tracheal stenosis (Cavaliere 2007). Predictive systems have been used to predict the duration of mechanical ventilation in various patient settings (Agle 2006; Gajic 2007; Légaré 2001; Sellers 1997), but many of these systems are not appropriately validated. Several other factors have also been shown, in studies, to provide indications for tracheostomy: neuromuscular disease, trauma, age, injury severity score, damage control laparotomy and others (Frutos-Vivar 2005; Goettler 2006). Some researchers have proposed that the decision to perform tracheostomy should be based on objective measures obtained from spontaneous breathing trials or from trials on weaning from mechanical ventilation (Freeman 2008). Thus, the development of predictive methods that can be tailored for each clinical condition would be a major advance in patient care.

Description of the intervention

Tracheostomy is a surgical procedure whereby an external artificial opening is made in the trachea (Stedman 1995). Several techniques are used to perform tracheostomy, including the classical standard surgical procedure completed in a surgical room and the percutaneous method performed at the patient's bedside (Friedman 2006; Gullo 2007; Pappas 2011; Schultz 2007). Surgical and percutaneous procedures are usually performed by different surgical specialists such as general; thoracic; ear, nose and throat (ENT); or maxillofacial surgeons, but percutaneous procedures are usually but not exclusively performed by surgeons and intensivists (Pappas 2011; Plummer 1989). A diversity of materials (equipment and designs) are used in performing tracheostomy (Björling 2007; Crimlisk 2006; Hess 2005). These can be associated with complications such as tracheal ulceration, distortion of soft tracheal tissue and airway obstruction (Tibballs 2006).

Plummer 1989 used the translaryngeal route for patients expected to be on mechanical ventilation for up to 10 days and tracheostomy for those on artificial ventilation for longer than 21 days; however, tracheostomy is usually performed between the 10th and 14th days of intubation (Armstrong 1998). Nowadays, opinions regarding the best time to perform tracheostomy are conflicting (Heffner 2003). Relevant studies vary in design and in the clinical condition examined (Ahmed 2007; Barquist 2006). To circumvent this, the literature offers two categories of 'early' and 'late' for the timing of tracheostomy. Unfortunately these categories are not precisely defined, and study authors may characterize different times as 'early' and 'late,' resulting in some overlap between the categories (Aissaoui 2007; Barquist 2006; Dunham 2006; Lesnik 1992). Conflicting evidence is available on the advantages of early over late tracheostomy. For example, some comparative studies have reported shorter hospital stays, lower mortality rates and other benefits with the use of early as compared with late tracheostomy (Arabi 2004; Rodriguez 1990). Conversely, Clec'h 2007 observed no differences in mortality in the ICU between patients undergoing early versus late tracheostomy.

How the intervention might work

Potential benefits of tracheostomy include lower airway resistance, easier and safer tracheal suction, greater patient comfort, better communication, improved oral feeding, faster weaning from the ventilator and lower rates of ventilator-associated pneumonia (Heffner 2001; Plummer 1989). On the other hand, some of the disadvantages of tracheostomy include dislodgement or obstruction, wound infection, scarring, a false passage, haemorrhage and subglottic and tracheal stenosis (Bartels 1998; Dollner 2002; Higgins 2007; Norwood 2000).

Why it is important to do this review

The present review is intended to systematically map available evidence on the timing of tracheostomy (early vs late) in mechanically ventilated, critically ill patients.

OBJECTIVES

To evaluate the effectiveness and safety of early (≤ 10 days after tracheal intubation) versus late tracheostomy (> 10 days after tracheal intubation) in critically ill adults predicted to be on prolonged mechanical ventilation with different clinical conditions.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized (RCTs) and quasi-randomized controlled trials (QRCTs) published in any language. We included studies published in abstract form if sufficient information regarding their methods and results was provided. We approached the principal authors for additional information when necessary.

Types of participants

Inclusion criteria

1. Critically ill patients (for whom death is possible or imminent).
2. Patients expected to be on prolonged mechanical ventilation.
3. Adults (≥ 18 years).

We defined prolonged mechanical ventilation as ventilation provided for 24 hours to 21 consecutive days, six or more hours per day (Divo 2010; Shirzad 2010).

Exclusion criteria

1. Anatomical anomalies of the neck that would impair the tracheostomy procedure.
2. Previous tracheostomy.
3. Coagulation disturbances (e.g. thrombocytopenia).
4. Soft tissue infection of the neck.

Types of interventions

We considered the following comparison arms.

1. Early tracheostomy, if no serious attempt was made to wean the patient from the ventilator (tracheostomy based only on clinical or laboratory results and performed from two days to 10 days after intubation).
2. Late tracheostomy, if weaning had not been successful; performed later than 10 days after intubation.

Types of outcome measures

We considered all outcome measures reported in the primary studies. For each outcome, we accepted the definition used by the study authors. We discussed when necessary limitations such as use of non-validated instruments for evaluation or a divergence of definitions.

Primary outcomes

1. Mortality (time to mortality or frequency of deaths at any time point: in hospital, in ICU, or after discharge).
2. Duration of artificial ventilation.

Secondary outcomes

1. Length of stay in ICU (or frequency of tracheostomy at any time point).
2. Ventilator-associated pneumonia at any time point.
3. Laryngotracheal lesions at any time point (in epiglottis, vocal cord, larynx; subglottic ulceration and inflammation; stenosis).

For details about definitions, see Appendix 1 (Glossary of terms).

Search methods for identification of studies

Electronic searches

In this updated review, we searched the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 8); MEDLINE (via Ovid) (1966 to August 2013); EMBASE (via Ovid) (1974 to August 2013); LILACS (1986 to August 2013); PEDro (Physiotherapy Evidence Database) at http://www.pedro.fhs.usyd.edu.au) (1999 to August 2013) and CINHAL (via EBSCO host, 1982 to August 2013). We reran the search in October 2014. We will deal with any studies of interest when we update the review.

The original search was run in December 2010 (Gomes Silva 2012).

The search strategy for MEDLINE included terms for clinical conditions and interventions as well as their synonyms (Appendix 2). This strategy was modified as required for other databases (Appendix 3 (CENTRAL); Appendix 4 (EMBASE); Appendix 5 (LILACS); Appendix 6 (Current Controlled trials); Appendix 7 (PEDro); and Appendix 8 (CINAHL)). We used a highly sensitive search filter for randomized controlled trials in databases for which this was necessary (MEDLINE, EMBASE and LILACS) to optimize the search process (Higgins 2011b).

We imposed no language restrictions.

Searching other resources

We handsearched the references of relevant articles including narrative reviews and non-randomized controlled studies on mechanical ventilation.

We searched for ongoing randomized controlled trials in the Current Controlled Trials database at http://www.controlled-trials.com/.

Data collection and analysis

Selection of studies

Two review authors (HS and BNGA) independently analysed the titles and abstracts of publications obtained through the search strategy. We (RA and BNGA) acquired full-text versions of all studies that met our inclusion criteria.

Data extraction and management

We (RA and BNGA) extracted data using a specially designed data extraction sheet (Appendix 9) that contained information about methods (study design), participants, interventions (e.g. surgical procedures, materials) and results. We resolved all disagreements by consensus. We contacted the authors of the primary studies to request further information about methodology and participants, when necessary. Two review authors (RA and BNGA) abstracted the data and entered all into Review Manager (RevMan 5.1). A third review author (HS) rechecked all entries.

Assessment of risk of bias in included studies

Two review authors (RA and BNGA) assessed all included studies for methodological quality based on the criteria put forth in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

1. Was the random allocation sequence adequately generated?
2. Was allocation adequately concealed?
3. Was knowledge of the allocated interventions adequately prevented for data collectors, or were data collectors independent of the researchers who planned the study (blinding)?
4. Were incomplete outcome data adequately addressed?
5. Are reports of the study free of the suggestion of selective reporting?
6. Was the study apparently free of other bias?

We classified each of the items as low risk of bias, high risk of bias or unclear risk of bias.

Because of the nature of the interventions of interest for this systematic review, we considered item 3 (blinding) only at the data collection level.

Measures of treatment effect

For comparable studies, we expressed dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs) using the random-effects model (Deeks 2001a). We calculated the number needed to treat for an additional beneficial outcome (NNTB) when risk differences were statistically significant (Christensen 2006). For continuous data, we calculated the mean difference using the random-effects model. We planned to calculate the standardized mean difference when trials assessed the same outcome but used different instruments or scales (Deeks 2001b).

Unit of analysis issues

We based the unit of analysis on the individual participant (unit to be randomly assigned to interventions to be compared) (Higgins 2011a). We did not expect to find cross-over study designs because of the characteristics of the interventions.

Dealing with missing data

Irrespective of the type of data obtained, we planned to report dropout rates in the Characteristics of included studies table and to perform intention-to-treat (ITT) analyses only for dichotomous data (Deeks 2005).

Assessment of heterogeneity

We presented data using a random-effects model (DerSimonian 1986). We quantified inconsistency among pooled estimates by using the Chi^2 statistic; for heterogeneity we used the I^2 statistic (where $I^2 = [(Q - df)/Q] \times 100\%$; Q is the Chi^2 statistic and df is its degrees of freedom). This illustrates the percentage of variability in effect estimates resulting from heterogeneity rather than from sampling error (Higgins 2002; Higgins 2003). We decided that we would not combine studies in a meta-analysis when they presented considerable statistical heterogeneity as indicated by the I^2 statistic, according to the following thresholds.

1. 0% to 40%: may not be important.
2. 30% to 60%: may represent moderate heterogeneity.
3. 50% to 90%: may represent substantial heterogeneity.
4. 75% to 100%: shows considerable heterogeneity.

Assessment of reporting biases

We planned to assess publication bias or a systematic difference between smaller and larger studies (small-study effects) by preparing a funnel plot (trial effect vs trial size) when sufficient numbers of studies were available (Copas 2000).

Data synthesis

We synthesized qualitative information relative to methods, risk of bias, description of participants and outcomes measures and presented them in the Characteristics of included studies table. For quantitative data, we planned to use the random-effects model in the meta-analysis because of substantial clinical and methodological heterogeneity between studies, which by themselves could generate substantial statistical heterogeneity. When data from primary studies were not parametric (e.g. effects were reported as medians, quartiles, etc) or were reported without sufficient statistical information (e.g. standard deviations, numbers of participants, etc), we planned to insert them into an 'Appendix.' Additionally, each clinically relevant estimate of effect was presented in Summary of findings for the main comparison (Schünemann 2009).

Subgroup analysis and investigation of heterogeneity

We planned to stratify our analysis by using the following independent variables, which are expected to be associated with heterogeneity.

1. Clinical condition (e.g. trauma, preexisting neurological and lung diseases).
2. Different timing of 'early' and 'late' tracheostomies.
3. Type of tracheostomy, such as percutaneous or surgical tracheostomy.

We planned to conduct these analyses only if data were available in the report or were obtained by contacting the main authors of the studies. In spite of the number of defined subgroup analyses, the eventual statistical heterogeneity observed across subgroups would not be assumed to show a true causal relationship between dependent and independent variables, but only to generate a hypothesis to be tested in future trials.

Sensitivity analysis

If an adequate number of studies were identified, we planned to perform a sensitivity analysis to explore the causes of heterogeneity and the robustness of study results. We planned to consider the following factors when performing the sensitivity analysis: quality of allocation concealment (adequate or unclear or inadequate); blinding (adequate or unclear or inadequate or not performed); analysis using both random-effects and fixed-effect models; intention-to-treat analysis and available case analysis (only for dichotomous data). Inclusion of studies with different timing for early and late tracheostomies than was presented in our inclusion criteria was considered in a sensitivity analysis.

We did not plan to present the results obtained from subgroup and sensitivity analyses as conclusions. We intended that they would be used for generation of hypotheses that would be tested in future adequately designed studies.

RESULTS

Description of studies

Results of the search

The search resulted in retrieval of 1433 studies in the first version of this systematic review (Gomes Silva 2012). In this updated version, the search yielded 2006 citations across all electronic databases. We excluded duplicate references and thus retrieved 1466 unique citations. Of these citations, we excluded a further 1359 on the basis of title and abstract, because they were not specifically related to the 'timing of tracheostomy.' From the remaining 107 studies, we excluded a further 84 because of their study design. Thus, 23 studies had the potential to be included in the review (Figure 1). Of those 23 studies, four were ongoing RCTs and one has been awaiting assessment. We contacted the main authors of one of the remaining 18 studies to request further information on the comparison groups (Blot 2008). This study was later excluded for reasons outlined in the Characteristics of excluded studies table.

We reran the search in October 2014 and retrieved 204 new citations, with 18 studies referring to timing of tracheostomy. Of those studies, two RCTs were of interest and are awaiting assessment (Dunham 2014; Mohamed 2014) (see Characteristics of studies awaiting classification). We will deal with them in the next update of this review.

At the title and abstract stage of selection, the Kappa coefficients (Kc) used to evaluate concordances between the two observers (RA and BNGA) were calculated in databases with at least one discordance (Latour 1997). At the first study selection, concordance levels were considered excellent for three databases—Kc = 0.91 (CENTRAL), Kc = 0.85 (EMBASE), Kc = 0.94 (MEDLINE)—and good

for CINAHL (Kc = 0.63). For the other databases as well, and in the updated version of this review, no discordance between observers was noted.

Included studies

In the first version (Gomes Silva 2012), we included four studies (Barquist 2006; Dunham 1984; Rumbak 2004; Terragni 2010). In this updated version, we included eight studies (Barquist 2006; Bösel 2013; Dunham 1984; Rumbak 2004; Terragni 2010; Trouillet 2011; Young 2013; Zheng 2012), with a total of 1977 participants randomly assigned to early or late tracheostomy. The authors of four of the RCTs revealed that they had received support from different institutions that did not participate in preparing the content of the final publications, including design, conduct, analysis, interpretation and writing of the studies (Terragni 2010; Trouillet 2011; Young 2013; Zheng 2012). These studies were diverse with respect to their inclusion criteria, methods of tracheostomy and outcome measures (see Characteristics of included studies).

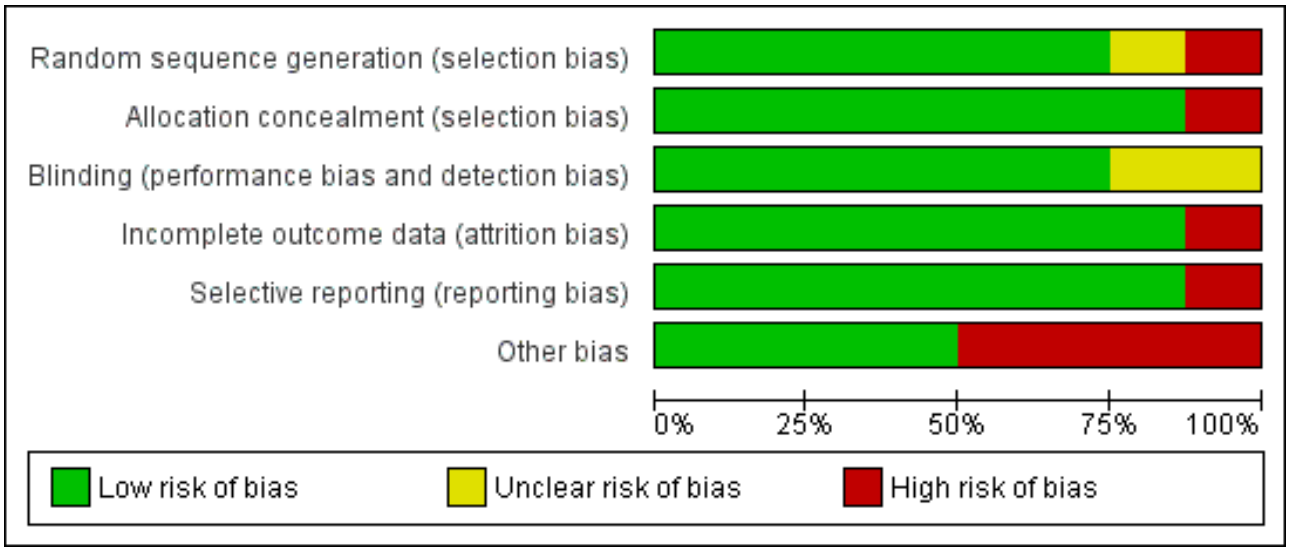
Excluded studies

We excluded seven studies because they compared early tracheostomy versus prolonged endotracheal intubation (Blot 2008; Bouderka 2004; El-Naggar 1976; Fayed 2012; Saffle 2002; Stauffer 1981; Sugerman 1997). In one quasi-randomized study, late tracheostomy was performed eight days after admission (< 10 days), thus breaching the selection criteria (> 10 days after intubation) for this review (Rodriguez 1990). Another study performed late tracheostomy ≥ 6 days after intubation (before 10 days) (Koch 2012). For further details, see the Characteristics of excluded studies table.

Risk of bias in included studies

We paid special attention to descriptions of randomization and allocation concealment, as the absence of adequate methodological aspects is associated with biased estimated effects (Schulz 1995). A synthesis of the assessment of all items of methodological quality described below is presented in Figure 2 and Figure 3.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Randomization

Five studies (Barquist 2006; Bösel 2013; Terragni 2010; Trouillet 2011; Zheng 2012) reported computer-generated randomization or automated 24-hour telephone service (Young 2013), which we considered to possess low risk of bias. Neither study found significant differences between comparison groups in terms of baseline characteristics.

Dunham 1984 referred to randomization based upon the last digit of the patient's hospital number—a method that we deemed indicative of resulting in high risk of bias (quasi-randomized study).

Rumbak 2004 did not explicitly report the method of randomization; thus the study was considered to reflect moderate risk of bias.

Allocation concealment

Four studies (Barquist 2006; Bösel 2013; Rumbak 2004; Zheng 2012) utilized envelopes to conceal the allocation of participants. Terragni 2010 and Trouillet 2011 clearly reported a centralized process of randomization. Young 2013 used an automated 24-hour telephone service based on an algorithm that minimized the imbalance between groups.These seven studies were therefore considered to have low risk of bias. However, Dunham 1984, a quasi-randomized study, was considered to possess high risk of bias associated with allocation concealment.

Blinding

In six studies (Barquist 2006; Dunham 1984; Rumbak 2004; Trouillet 2011; Young 2013; Zheng 2012), investigators clearly did not blind participants or therapists, or no information was given as to whether the data collectors were independent from the researchers who designed the study, or whether they were blinded to the

allocations. However, these studies were considered to have low risk of bias associated with potential knowledge about the allocated interventions (blinding) because all primary outcomes analysed in this systematic review were considered objective, as suggested in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Additionally, Bösel 2013 and Terragni 2010 used blinded or independent data collectors. Consequently, these studies were also deemed as possessing low risk of bias associated with blinding.

Incomplete outcome data

Six studies (Barquist 2006; Bösel 2013; Rumbak 2004; Trouillet 2011; Young 2013; Zheng 2012) were considered to have low risk of bias associated with incomplete outcome data resulting from low dropout rates, use of intention-to-treat (ITT) analysis and clear participant flows. At the first version of this systematic review, we considered that the numbers of participants from randomization to analysis of each outcome were not clearly reported for each of the comparison groups in Terragni 2010. Therefore this study was considered to have high risk of bias. However, we could now identify that ITT analysis was properly performed by the study authors. Withdrawals at one year of follow-up consisted of the following: n = 10 (4.78%) in the early tracheostomy group, and n = 4 (1.9%) in the late tracheostomy group.

Dunham 1984 was considered to possess high risk of bias as, after randomization, only participants who were intubated for at least seven days were included in the study. The study authors did not indicate the percentages or numbers of participants not considered for analysis after randomization.

Selective reporting

Seven studies were considered to have low risk of bias based on the relevant outcomes considered for evaluation and the absence of suspected selective outcome reporting (Barquist 2006; Bösel 2013; Rumbak 2004; Terragni 2010; Trouillet 2011; Young 2013; Zheng 2012). Dunham 1984 was deemed to be a study with high risk of systematic error resulting from the absence of clinically relevant outcomes (such as mortality rates).

Other potential sources of bias

Dunham 1984 evaluated 50% of participants at four to six months after extubation. The remaining participants were interviewed 12 months after extubation, but the exact number of participants per comparison group was not specified. No indication was given of the absence of substantial differences between comparison groups at baseline (comparable groups).

Seven studies showed no other suspected potential for bias (Barquist 2006; Bösel 2013; Rumbak 2004; Terragni 2010; Trouillet 2011; Young 2013; Zheng 2012).

Effects of interventions

See: **Summary of findings for the main comparison** Early vs late tracheostomy for critically ill patients

Primary outcomes

Mortality

Evidence of moderate quality demonstrates that mortality rate at the longest follow-up time available in seven studies combined was lower in the group given early tracheostomy (47.1%; 448/950) than in the group given late tracheostomy (53.2%; 507/953), with a statistically significant risk ratio (RR) of 0.83 (95% confidence interval (CI) 0.70 to 0.98; P value 0.03; number needed to treat for an additional beneficial outcome (NNTB) ≅11; Analysis 1.1) (Barquist 2006; Bösel 2013; Rumbak 2004; Terragni 2010; Trouillet 2011; Young 2013; Zheng 2012).

With regard to mortality at 30 days of follow-up, the review authors have opted to present results from individual studies because the inconsistency test may represent substantial statistical heterogeneity between studies (I^2 = 77%). Thus, Rumbak 2004 is the only study that demonstrated a significant difference between groups, with a lower mortality rate in the early tracheostomy group (RR 0.51, 95% CI 0.34 to 0.78; P value 0.002; NNTB = 3.33); Young 2013 and Zheng 2012 did not demonstrate significant differences between groups (Analysis 1.3 and Table 1, lines 1.1.1 to 1.1.3). At 180 days of follow-up, Bösel 2013 reported a lower percentage of mortality in the early tracheostomy group (RR 0.44, 95% CI 0.23 to 0.85; P value 0.01; NNTB = 2.8) (Table 1, line 1.1.5). The same study author reported a statistically significant difference, with a lower mortality rate until ICU discharge, in the early tracheostomy group (RR 0.21, 95% CI 0.07 to 0.67; P value 0.008; NNTB = 2.7), but Young 2013 found no significant differences between groups (RR 0.98, 95% CI 0.81 to 1.19; P value 0.83) (Analysis 1.6 and Table 1, lines 1.1.7 and 1.1.8). The two studies were not combined in a meta-analysis because the inconsistency test (I^2 = 85%) may represent substantial heterogeneity between studies (Bösel 2013; Young 2013).

Studies did not demonstrate significant differences between early and late tracheostomy groups for mortality at 28 days (Analysis 1.2), 60 days (Analysis 1.4), 90 days (Table 1, line 1.1.4) and one and two years of follow-up (Analysis 1.5 and Table 1, line 1.1.6, respectively), nor until the time of ICU or hospital discharge (Table 1, lines 1.1.8. and 1.1.9, respectively).

Duration of artificial ventilation

Trouillet 2011 and Zheng 2012 evaluated mean ventilator-free days until 28 days of follow-up, but the meta-analysis resulted in no statistically significant estimated effect (mean difference (MD) 1.62, 95% CI −0.01 to 3.25; P value 0.05; I^2 = 0%; Analysis 1.7). Rumbak 2004 and Trouillet 2011 measured mean days of mechanical ventilation, but their results cannot be combined in a meta-analysis because substantial statistical heterogeneity has been observed between them (I^2 = 92%) (Analysis 1.8). Rumbak 2004 reported a statistically significant mean reduction of 9.8 days of mechanical ventilation (95% CI -11.48 to -8.12; P value < 0.00001) in the early tracheostomy group (Table 1, line 1.2.1), and Trouillet 2011 found a statistically insignificant reduction of -1.40 days (95% CI -5.65 to 2.85; P value 0.52), also in the early group (Table 1, line 1.2.2). No statistically significant differences between comparison groups were noted in other ways of measuring duration of artificial ventilation, as reported by Trouillet 2011 (ventilator-free days during one to 60 days, Table 1, line 1.2.3; ventilator-free days during one to 90 days, Table 1, line 1.2.4) and Dunham 1984 (intubation for longer than 21 days, Table 1, line 1.2.5). Terragni 2010 found a statistically significant difference in ventilator-free days (at day 28) in the early tracheostomy group (median of 11 days, interquartile range zero to 21) as compared with the late tracheostomy group (median of six days, interquartile range zero to 17) (P value 0.02) (Table 2, line 1). Although Bösel 2013 found

a median reduction of three days of ventilation time in the early tracheostomy group, the difference was not statistically significant (P value 0.23) (Table 2, line 2).

Secondary outcomes

Length of ICU stay

Two studies measured the mean number of days in the ICU. Their findings could not be combined in a meta-analysis, however, because substantial heterogeneity between them was observed (Analysis 1.9). Thus, Rumbak 2004 showed a clinically and statistically relevant lower mean number of days in the ICU in the early tracheostomy group than in the late tracheostomy group (MD -11.40 days, 95% CI -12.42 to -10.38; P value < 0.00001; Table 1, line 2.1.1). Otherwise, Trouillet 2011 found a slightly lower mean number of ICU days in the early tracheostomy group but no statistically significant differences between groups (MD -1.60 days, 95% CI -7.40 to 4.20; P value 0.59; Table 1, line 2.1.2). Two other studies combined in a meta-analysis showed a significantly higher probability of discharge from ICU at 28 days of follow-up in the early tracheostomy group (140/267; 52.4%) than in the late tracheostomy group (111/271; 40.9%), with an RR of 1.29 (95% CI 1.08 to 1.55; P value 0.006; NNTB = 8.3) (Analysis 1.10). Additionally, Terragni 2010 and Bösel 2013 found no differences between comparison groups that were clinically or statistically relevant (Table 2, lines 3 and 4), but Zheng 2012 observed a clinically and statistically significant difference in ICU-free days at day 28 between the early tracheostomy group (median 8.0 days, interquartile range five to 12 days) and the late tracheostomy group (median 3.0 days, interquartile range zero to 12 days) (P value 0.048) (Table 2, line 5).

Pneumonia

The combination of all studies measuring pneumonia rates in a meta-analysis (Dunham 1984; Rumbak 2004; Terragni 2010; Trouillet 2011; Zheng 2012) yielded substantial statistical heterogeneity (I^2 = 71%). By consensus, we have decided to present the data on pneumonia in a forest plot with isolated estimated effects from the studies, excluding a meta-analysis (Analysis 1.11). The combined percentage of pneumonia events in the early tracheostomy group is 25.5%, versus 32.6% in the late tracheostomy group. Rumbak 2004 and Zheng 2012 showed a significantly lower probability of pneumonia in study participants allocated to the early tracheostomy group, with estimated effects of RR 0.20 (95% CI 0.06 to 0.66; P value 0.008; NNTB = 5; Table 1, line 2.2.2) and RR 0.60 (95% CI 0.37 to 0.96; P value 0.03; NNTB = 5; Table 1, line 2.2.5), respectively. Terragni 2010, which did not include patients with pneumonia at study entry, reported an RR of 0.69 in favour of the early tracheostomy group but without statistical significance (95% CI 0.45 to 1.05; P value 0.08). Two studies (Dunham 1984; Trouillet 2011) found higher percentages of participants with pneumonia in the early tracheostomy group but without statistical significance, as observed in the following estimations of RR 1.18 (95% CI 0.77 to 1.79; P value 0.45) (Table 1, line 2.2.1) and RR 1.04 (95% CI 0.78 to 1.40; P value 0.77) (Table 1, line 2.2.4), respectively.

Laryngotracheal lesions at any time point (in epiglottis, vocal cord, larynx; subglottic ulceration and inflammation; stenosis)

The studies included in this systematic review found no clinically or statistically relevant differences between early and late tracheostomies in occurrence of the following postoperative adverse events: stoma inflammation; postoperative and intraoperative minor and major bleeding; pneumothorax; subcutaneous emphysema; tracheo-oesophageal fistula and cannula displacement or need for replacement (Terragni 2010); significant laryngotracheal pathology; respiratory sepsis; major complications; complications (Dunham 1984); percentage of tracheal stenosis, irrespective of severity (in-hospital); tracheal stenosis > 50 (10 weeks post intubation) (Rumbak 2004); self-extubation (Rumbak 2004) and sternal wound or stoma infection (Terragni 2010; Trouillet 2011). For details on the estimated effects, please refer to Table 1 (lines 2.3.1 to 2.3.4; 2.3.6 to 2.3.9; and 2.3.12 to 2.3.16) and Analysis 1.12.

The following events occurred significantly more often in the early tracheostomy group: tracheal stenosis with a severity score from zero to 20 in hospital and 10 weeks after intubation; and tracheal stenosis, irrespective of severity, 10 weeks after intubation (Rumbak 2004, Table 1, lines 2.3.10, 2.3.14 and 2.3.17). Bösel 2013, however, found a significantly lower proportion of participants with postoperative bleeding in early tracheostomy (Table 1, line 2.3.5).

Other potentially relevant outcomes not planned in the protocol of this systematic review

Of the 43 outcomes with potential clinical relevance that were not previously planned in this systematic review, 18 outcomes showed statistically significant estimated effects in favour of early tracheostomy. These outcomes included recannulation, reintubation, nursing evaluation, nutrition, self-extubation, successful weaning, bed-to-chair transfer, cannula displacement and need for replacement as aspects relative to duration of sedation, as shown in Appendix 10 (lines 15 to 24; 26 to 29; 33, 35 and 36) and Appendix 11 (lines 9 and 11).

Sensitivity analysis

Because of the relative paucity of included studies, we performed a sensitivity analysis just for mortality at the longest follow-up time available in the studies. This analysis was performed by including one RCT and one quasi-RCT that had been excluded from this systematic review (Koch 2012; Rodriguez 1990, respectively). These studies were excluded because late tracheostomies (< 10 days) did not meet our inclusion criteria. This sensitivity analysis showed very similar estimate effects upon their exclusion (please refer to Analysis 1.1) with an RR of 0.84 (95% CI 0.73 to 0.98; P value 0.02; I^2 = 40%; NNTB = 12.5; n = 206 participants).

DISCUSSION

Summary of main results

Primary outcomes

At the longest follow-up time available in the studies, moderate-quality evidence from seven randomized controlled trials showed a significant mortality rate in the early tracheostomy group as compared with the late tracheostomy group (Barquist 2006; Bösel 2013; Rumbak 2004; Terragni 2010; Trouillet 2011; Young 2013; Zheng 2012); it was necessary to treat for an additional beneficial outcome (NNTB) approximately 11 critically ill patients with early tracheostomy to prevent one death. The review authors paid special attention to the sensitivity analysis that tested the effects of studies excluded because their times of tracheostomy did not meet our inclusion criteria. This sensitivity analysis was done for

mortality at the longest follow-up time available in the studies. Although the results of this sensitivity analysis (please see Effects of interventions at sensitivity analysis) may not be considered in our conclusions, they were very similar to the findings of the meta-analysis of included studies, in spite of the inclusion of two additional excluded randomized controlled trials (RCTs) (Analysis 1.1). At 30 days of follow-up, only one study (Rumbak 2004) out of three (Rumbak 2004; Young 2013; Zheng 2012) demonstrated a significant difference between groups, with a lower mortality rate in the early tracheostomy group; thus, it was necessary to treat approximately three critically ill participants with early tracheostomy to prevent one death. Additionally, significant differences favouring the early tracheostomy group were reported by Bösel 2013 at 180 days and until ICU discharge; it was necessary to treat approximately three participants with early tracheostomy to prevent one death at both times of follow-up. No study demonstrated significant differences between early and late tracheostomy groups for mortality at 28, 60 and 90 days, and at one and two years of follow-up, nor until both ICU and hospital discharge.

Two studies combined in a meta-analysis contributed to the moderate-quality evidence found to support the absence of differences between comparison groups for mean ventilator-free days until 28 days of follow-up (Trouillet 2011; Zheng 2012). Individual studies, however, showed significantly less mean time spent in mechanical ventilation in the early tracheostomy group, with a mean reduction of 9.8 days in Rumbak 2004 and, in Terragni 2010, a longer median time in the early tracheostomy group of five ventilator-free days at 28 days of follow-up. Other individual studies showed non-significantly less time on mechanical ventilation in the early tracheostomy group (Bösel 2013; Dunham 1984; Trouillet 2011). In addition, Terragni 2010 demonstrated that early tracheostomy is significantly associated with a higher rate of successful weaning—an outcome related closely to time spent on mechanical ventilation.

Secondary outcomes

With respect to secondary outcomes, two studies combined in a meta-analysis showed a significantly higher probability of discharge from the ICU at 28 days of follow-up in the early tracheostomy group; it was necessary to offer the early tracheostomy to approximately eight participants to account for one discharge from ICU at day 28 (Terragni 2010; Zheng 2012). One study showed a relevant mean reduction of approximately 11 days in the ICU in the early as opposed to the late tracheostomy group (Rumbak 2004). Another important difference of a median of five ICU-free days was observed by Zheng 2012 in the early tracheostomy group. Bösel 2013, Terragni 2010 and Trouillet 2011, however, found insignificant differences in the time spent in the ICU: approximately one day.

No definitive evidence demonstrated that any one treatment is associated with lower probability of pneumonia, possibly because of the large heterogeneity between studies (Dunham 1984; Rumbak 2004; Terragni 2010; Trouillet 2011; Zheng 2012). Terragni 2010, in fact, unlike the other studies, excluded patients with chronic obstructive pulmonary disease and pneumonia at study entry.

Laryngotracheal lesions were observed significantly more frequently in participants who had undergone early tracheostomy as measured by tracheal stenosis (Rumbak 2004), but Bösel 2013 found a significantly lower probability of postoperative bleeding in participants who had undergone early tracheostomy.

Overall completeness and applicability of evidence

The whole findings of this systematic review are no more than suggestive of the superiority of early over late tracheostomy, because no information is available on high quality for specific subgroups with particular characteristics. Thus, our results suggest, but not definitively, that it would be necessary to treat (NNTB) approximately 11 patients to prevent one death (Barquist 2006; Bösel 2013; Rumbak 2004; Terragni 2010; Trouillet 2011; Zheng 2012). It is important to consider that available studies showed significant (Rumbak 2004; Terragni 2010) to little benefit (Bösel 2013; Dunham 1984; Trouillet 2011; Zheng 2012) of early tracheostomy for time spent on mechanical ventilation, and one study demonstrated that early tracheostomy was significantly associated with a higher rate of successful weaning—an outcome related closely to time spent on mechanical ventilation (Terragni 2010). Four studies suggested a possible but not definitive benefit of early tracheostomy for time spent in the ICU (Bösel 2013; Rumbak 2004; Terragni 2010; Zheng 2012). Thus, such results would outweigh the possibly higher risk of tracheal stenosis in the early tracheostomy group, which was reported only by Rumbak 2004.

Quality of the evidence

According to Summary of findings for the main comparison, the quality of the evidence was considered moderate for mortality at the longest follow-up time available in the studies. Besides clinical heterogeneity, which is a condition naturally present among critically ill patients, the main suspected reason to downgrade the quality of evidence was the influence of three larger trials with more modest and statistically non-significant effect estimates (Terragni 2010; Trouillet 2011; Young 2013). Although small trials are prone to stronger estimate effects (Pereira 2012), it is far from assumed that they are inherently flawed (Batterham 2013). Moreover, Ioannidis 1998 considered that there exist more divergences between meta-analyses and large trials published in the more persuasive scientific journals, and that the latter tend to be preferred over meta-analyses. Additionally, some study authors have indicated that when results from individual studies are fundamentally in the same direction (consistency across studies), the meta-analysis merits greater confidence, and they criticize those who look for strict "black and white" conclusions in scientific research (Cook 1995; Hill 1965; McCormack 2013).

As yet we have not included sufficient studies to enable us to explore publication bias. This bias can be considered a possibility because, in virtually all areas of knowledge, some investigators do not make their studies available, particularly those studies that show no effect (Song 2010). Apart from mortality, It was possible, however, to detect distinct qualities of evidence for the same outcomes as measured in different ways. For example, the quality of evidence of the specific outcome of ventilator-free days at 28 days of follow-up was graded as moderate, and the outcome of mean days of mechanical ventilation until 60 days of follow-up was considered to be of very low quality. Such a large divergence in the definitions of outcomes has been crucial in downgrading the quality of available evidence on this research question.

Potential biases in the review process

A high-sensitivity search strategy was used in this systematic review so as to avoid missing any randomized controlled trials that compared early versus late tracheostomy in critically ill patients. We prevented language bias by not imposing language restrictions upon the search. Other studies have been conducted but have not yet been published (Dumire 2008; Huttner 2010; Kluge 2009; Ranieri 2009), and their results may improve the evidence in this area. Such ongoing studies will probably be included in future versions of this review once their results have been made available.

Agreements and disagreements with other studies or reviews

The findings of our previous systematic review and of the reviews by Dunham 2006 and Griffiths 2005 did not consistently support either early or late tracheostomy for reducing mortality. Newly available studies, however, have helped prove, although still not definitively, the potential benefits of early tracheostomy as compared with late tracheostomy for mortality. Another systematic review carried out by Shan 2013 clearly supports the choice of early tracheostomy for reducing length of ICU stay, duration of mechanical ventilation and mortality, but the results apparently have been overestimated as a result of the inclusion of observational studies. In this sense, Scales 2008, in a large observational study involving more than 10,000 participants, showed that early tracheostomy is associated with significant advantages over late tracheostomy in terms of mortality for critically ill patients. Previous systematic reviews, as well as other observational studies and non-randomized controlled trials with lower methodological rigour, have also showed decreased time spent on ventilatory support (Arabi 2004; Arabi 2009; Blot 1995; Dunham 2006; Gandía-Martínez 2010; Griffiths 2005; Lesnik 1992; Zagli 2010), decreased time in the ICU (Arabi 2004; Arabi 2009, Gandía-Martínez 2010; Griffiths 2005; Lesnik 1992; Zagli 2010) and at the hospital (Arabi 2004; Arabi 2009; Blot 1995) and lower probabilities of pneumonia (Gandía-Martínez 2010; Lesnik 1992) and extubation (El-Naggar 1976) with early tracheostomy than with late tracheostomy. All of these results have been observed in the face of large clinical, regional, methodological and chronological diversity among studies.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence in this Cochrane review is considered to be of moderate quality but is not more than suggestive of recommending early (as against late) tracheostomy for reducing mortality among critically ill patients on prolonged mechanical ventilation. However, the available evidence should be considered with caution; information is insufficient to permit conclusions about any subgroup or individual characteristic(s) potentially associated with the best indications for early or late tracheostomy because clinical heterogeneity is a characteristic inherent to patients in the ICU.

Implications for research

Additional high-quality randomized controlled trials are necessary to better evaluate possible differences between early and late tracheostomy for critically ill patients. Some trials have already begun, and we are awaiting their results to produce updated versions of this systematic review. Researchers would contribute significantly to improving the evidence, by considering the following outcome measures: mortality rates up to 12 months of follow-up, time spent on mechanical ventilation, length of hospital stay and ICU stay. They should also consider other potentially relevant outcomes such as successful weaning, pneumonia and costs. However these outcomes should be standardized to allow their inclusion in meta-analyses. All investigators interested in this area of research should work together to make their raw data available. This would allow more precise indications to better identify which patients might benefit from an early tracheostomy.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Barquist 2006

Methods	Study design: parallel randomized controlled trial with intention-to-treat analysis and sample size based on the following information: A total of 140 participants would be needed if the SD was nine ventilator days, the difference between means was three days and the power was set at 90% Locale/Setting: Division of Trauma and Surgical Critical Care, DeWitt Daughtry Family Department of Surgery, University of Miami School of Medicine, Miami, Florida
Participants	1. N = 60 (early tracheostomy, n = 29/late tracheostomy, n = 31) 2. Age range, years: 18 to 87/mean age: 51.8 (whole sample) 3. Gender: 46 male/14 female 4. Ventilator-dependent patients 5. Traumatic injury as the proximate cause of their ventilator dependence 6. Intubated at least 3 days when they were 7 days after admission to the Trauma ICU
Interventions	1. Early tracheostomy: before day 8 2. Late tracheostomy: after day 28 All tracheostomies (early and late) were performed by the open surgical technique
Outcomes	1. Mortality rates (time of data collection was not explicitly referred to by the study authors) 2. Mean ICUfree days at 20 days 3. Mean ventilation-free days at day 30 (with extubation performed after spontaneous breathing trial (CPAP at 5 cm water pressure with 5 cm water pressure support for 30 minutes) with predefined criteria for passing (pO_2 greater than 55 mm Hg, respiratory rate less than 35 breaths/min and no respiratory acidosis)) 4. Mean ICU-free days at day 30 5. Ventilator-associated pneumonia at any time point (CDC criteria: Centers for Disease Control: elevated WBC, fevers, CXR infiltrate and bronchoalveolar lavage (BAL) culture with greater than 10,000 colony-forming units per millilitre (CFU/mL)) 6. Single superficial surgical site infection 7. Major complications related to the tracheostomy (including stomal infection, stomal haemorrhage, major vascular injury, pneumothorax, subglottic stenosis and tracheo-oesophageal fistulae)
Notes	4 participants in the 'late' group had a surgical tracheostomy placed on days 17, 18, 19 and 21 to facilitate transfer to long-term care Method to predict prolonged artificial ventilation: not explicitly reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated table Study authors referred to no significant differences between comparison groups on baseline characteristics
Allocation concealment (selection bias)	Low risk	After consent was obtained, an envelope with the assigned group inside was opened
Blinding (performance bias and detection bias) All outcomes	Low risk	No information was provided on whether data collectors were independent from the researchers who designed the study or were blinded to the alloca-

Barquist 2006 *(Continued)*

		tions. All primary outcomes of this review were considered objective, specifically mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study authors carried out the intention-to-treat analysis according to the appropriate definition
Selective reporting (reporting bias)	Low risk	No selective outcome reporting was suspected, as relevant outcomes were evaluated
Other bias	High risk	Although times of follow-up were explicitly announced for only three outcomes (mean ICU-free days at 20 days, mean ventilation-free days at day 30, mean ICU-free days at day 30), study authors did not explicitly report follow-up times for the other outcome data

Bösel 2013

Methods	Study design: parallel randomized controlled trial with sample size based on the following information: If length of ICU stay in both groups differed for about 11 days, this difference could already be detected with the sample size of the pilot trial with a power of 64% (Student's t-test with a 2-sided type I error of 5%) Locale/Setting: Department of Neurology, Institute of Medical Biometry and Informatics (PS), Department of Neurosurgery (JON, AU), University of Heidelberg, Heidelberg, Germany; Department of Vascular Neurology, University of Tübingen, Tübingen, Germany (SP); Department of Neurology, Frankfurt Hoechst Hospital, Frankfurt, Germany (TS)
Participants	1. N = 60 (early tracheostomy, n = 30/late tracheotomy, n = 30) 2. Mean age, years: 61 3. Admission to neurological and neurosurgical services 4. Diagnosis of non-traumatic intracerebral haemorrhage (ICH), subarachnoid haemorrhage (SAH) or acute ischaemic stroke (AIS) 5. Intubated and expected need for mechanical ventilation support for at least 2 weeks, as based on a non-validated in-house assessment score and the judgement of 2 experienced neurological intensive care specialists 6. APACHE scores: median 16 (range 11 to 19) for early tracheostomy and median 17 (range 13 to 19) for late tracheostomy
Interventions	1. Early tracheostomy: percutaneous dilatational tracheostomy (PDT) within 3 days from intubation 2. Late tracheostomy: PDT between days 7 and 14 from intubation if extubation, although aimed for, was not possible until then
Outcomes	1. Duration of ICU dependence (days from admission to a predefined status that would allow discharge from ICU (absence of active infection, vasopressors, pulmonary and cardiac instability, etc.)) 2. Functional outcome (modified Rankin Scale at admission, at discharge and at 6 months from insult) 3. Mortality (death from any cause during ICU stay or within 6 months after admission) 4. Hospital LOS (days spent at our hospital from admission to discharge) 5. Accumulated duration of ventilation (sum of half-days on the ventilator until the participant was ventilator-independent for 24 hours) 6. Accumulated duration and quality of weaning (sum of half-days spent under the possible application of a weaning protocol, and spent within specific stepwise phases of such a protocol)

Bösel 2013 *(Continued)*

	7. Accumulated duration of analgosedation dependence (sum of half-days requiring the application of sedatives and analgesics, which are also specified) 8. Accumulated duration of vasopressor dependence (sum of half-days under vasopressor treatment) 9. Accumulated duration of antibiotic treatment (sum of half-days under antibiotic treatment) 10. Frequency of pneumonia (number of episodes (predefined by official German diagnostic criteria for pneumonia)) 11. Occurrence and duration of sepsis (number of episodes and duration of sepsis as predefined by diagnostic criteria) 12. Numbers and types of complications associated with the procedure (during 10 days post TT, numbers and types of complications related to TT (i.e. bleeding, malpositioning, malfunction, replacement demand, etc.)) 13. Costs of treatment (total ICU cost estimated by LOS and severity-derived diagnosis-related group (DRG) multiplicator of each individual participant)
Notes	Need for mechanical ventilation support for at least 2 weeks was based on a non-validated in-house assessment score and the judgement of 2 experienced neurological intensive care specialists

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomization was based on a computer-generated randomization list
Allocation concealment (selection bias)	Low risk	Simple randomization was done using opaque, sealed envelopes for masking as prepared by a trial-independent person
Blinding (performance bias and detection bias) All outcomes	Low risk	ICU management for both trial groups was based on in-house protocols and general guidelines to achieve fair homogeneity between groups. Long-term mortality and functional outcomes were adjudicated by an investigator masked to participant and TT time point, based on narratives from a separate telephone interview. ICU mortality and cause of death were additionally confirmed by an independent investigator on the basis of charts and reports in which information on airway management was concealed. Moreover, all primary outcomes of this review were considered objective, specifically mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were analysed
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes were reported by the study authors
Other bias	Low risk	None was suspected

Dunham 1984

Methods	Study design: parallel quasi-randomized controlled trial without intention-to-treat analysis Locale/Setting: The Shock Trauma Center of the Maryland Institute for Emergency Medical Services Systems (MIEMSS)
Participants	1. N = 74 (early tracheostomy, n = 34/late tracheotomy, n = 40) 2. Age range, years: 17 to 75 3. Intubation for at least 7 days

Dunham 1984 *(Continued)*

	4. Severe head injury 5. Respiratory insufficiency and/or a tenuous or incompetent airway secondary to maxillofacial injury
Interventions	1. The early group underwent transtracheal intubation at 3 to 4 days after initiation of translaryngeal intubation 2. Participants assigned to the late group had transtracheal intubation performed 14 days after initiation of translaryngeal intubation, if continued intubation was required Trachestomy (early and late) method: The incision was standardized as a vertical soft tissue incision and a vertical incision through the second and third tracheal rings and the upper half of the fourth ring without removal of any tracheal tissue
Outcomes	1. Significant laryngotracheal pathology (irrespective of type) that required surgery and/or prolonged tracheal intubation beyond that required for the participant's general condition 2. Respiratory sepsis (tracheitis, pneumonia, lung abscess and peristomal infection) 3. Major complications (not explicitly defined by study authors) 4. Complications (self-extubation, participant tolerance, respiratory hygiene, and aspiration) 5. Proportion of participants intubated for until up to 21 days
Notes	Method to predict prolonged artificial ventilation: Participants were randomly assigned to an early or late tracheostomy group If at the end of 48 to 72 hours of translaryngeal intubation, the attending surgeon believed that they needed at least 48 hours of additional tracheal intubation Gender: not informed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomization was based on the last digit of the patient's hospital number; even numbers constituted the early tracheostomy group, and odd numbers the late tracheostomy group Substantial differences in frequency of baseline characteristics were observed between comparison groups (rigid head injury, non-head injury and non-rigid head injury).
Allocation concealment (selection bias)	High risk	The method of sequence generation used in this study ideally permits anyone to foresee the group to which each of the participants would be allocated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information was provided on whether data collectors were independent from the researchers who designed the study or were blinded to the allocations
Incomplete outcome data (attrition bias) All outcomes	High risk	After randomization, only participants who were intubated for at least 7 days were included. Study authors did not inform percentages or numbers of participants not considered for analysis after randomization
Selective reporting (reporting bias)	High risk	Study authors did not report mortality
Other bias	High risk	Fifty per cent of participants were evaluated at 4 to 6 months after extubation; the remaining participants were interviewed 12 months after extubation, and the number of participants included in each comparison group was not indicated Statistical differences at baseline were not informed. No explicit information was provided about times of follow-up

Rumbak 2004

Methods	Study design: parallel randomized controlled trial without intention-to-treat analysis Locale/Setting: Medical Intensive Units at the Baptist Memorial Hospital, University of Tennessee, Memphis, TN, and Tampa General and the James A. Haley Veterans Administration Hospital, University of South Florida, Tampa, FL
Participants	1. N = 120 (early tracheostomy, n = 60/late tracheostomy, n = 60) 2. Mean age, years: 63 3. Gender: 65 male/55 female 4. Projected to need ventilation support for > 14 days 5. initial Acute Physiology and Chronic Health Evaluation (APACHE) II score > 25
Interventions	1. Tracheotomy within 48 hours after intubation 2. Late tracheotomy at days 14 to16 Participants from both groups were subjected to percutaneous dilatational tracheostomy procedure (PDT)
Outcomes	1. Mortality (at 30 days) 2. Mean intensive care stay 3. Days mechanically ventilated 4. Days sedated 5. Days on high-dose pressors 6. Pneumonia 7. Ventilator-associated pneumonia and death 8. Gastrointestinal bleed and death 9. Acute myocardial infarction and death 10.Pulmonary embolus and death 11.Intractable septic shock and death 12.Withdrawal of life support and death 13.Respiratory failure and death 14.Tracheal stenosis 0 to 20 (in-hospital) 15.Tracheal stenosis 21 to 50 (in-hospital) 16.Tracheal stenosis > 50 (in-hospital) 17.Tracheal stenosis 0 to 20 (10-week post intubation) 18.Tracheal stenosis 21 to 50 (10-week post intubation) 19.Tracheal stenosis > 50 (10-week post intubation) 20.Self-extubation
Notes	Method to predict prolonged artificial ventilation: not explicitly reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not explicitly reported Groups were similar in mean age, proportions of women and African Americans, APACHE II scores and underlying diseases
Allocation concealment (selection bias)	Low risk	Independent group randomization was placed in sequentially numbered envelopes to be opened once consent was signed

Rumbak 2004 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	No information was provided on whether data collectors were independent from the researchers who designed the study or were blinded to the allocations. However, all primary outcomes of this review were considered objective, specifically mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although no intention-to-treat analysis was performed, flow of participants within the study was clear
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes were reported by study authors
Other bias	High risk	Study authors (except SWS) performed the percutaneous dilatational tracheostomy Although the airways were assessed for oral, laryngeal and tracheal damage at 10 weeks post intubation, no explicit information was provided about time of follow-up for the other outcomes

Terragni 2010

Methods	Study design: parallel randomized controlled trial with intention-to-treat analysis Locale/Setting: Italian intensive care units Support: Regione Piemonte Ricerca Sanitaria Finalizzata
Participants	1. N = 419 (early tracheostomy, n = 209/late tracheostomy, n = 210) 2. Mean age, years: 61.5 3. Gender: 138 male/142 female 4. Mechanically ventilated for acute respiratory failure for 24 hours 5. Simplified Acute Physiology Score II between 35 and 65 6. Sequential organ failure assessment (SOFA) score > 5 7. Without pulmonary infection (estimated by a Clinical Pulmonary Infection Score (CPIS) < 6), chronic obstructive pulmonary disease, anatomical deformity of the neck (including thyromegaly) and cervical tumours; a history of oesophageal, tracheal or pulmonary cancer; previous tracheostomy; soft tissue infection of the neck; haematological malignancy; or pregnancy 8. $PaO_2 \leq 60$ mm Hg 9. Fraction of inspired oxygen (FiO_2) ≥ 0.5 10. Positive end-expiratory pressure (PEEP) ≥ 8 cm H_2O 11. Acute clinical condition requiring ventilatory support and still unresolved 12. SOFA score ≥ 5
Interventions	1. Early tracheostomy: after 6 to 8 days of laryngeal intubation 2. Late tracheostomy: after 13 to 15 days of laryngeal intubation Participants from both groups were subjected to percutaneous tracheostomy
Outcomes	1. Mortality (at 28 days) 2. Mortality (at 1 year) 3. Need for a long-term care facility 4. Ventilator-free days (at day 28) 5. ICU-free days (at day 28) 6. ICU discharge

Terragni 2010 *(Continued)*

7. Successful weaning
8. Hospital length of stay
9. Ventilator-associated pneumonia
10. Intraoperative adverse events (minor bleeding, significant bleeding, tube dislocation, hypoxaemia, arrhythmia, cardiac arrest)
11. Postoperative adverse events (stoma inflammation, stoma infection, minor bleeding, major bleeding, pneumothorax, subcutaneous emphysema, tracheo-oesophageal fistula, cannula displacement or need for replacement)

Notes	Method to predict prolonged artificial ventilation: mechanically ventilated for acute respiratory failure for 24 hours; Simplified Acute Physiology Score II between 35 and 65; sequential organ failure assessment (SOFA) score ≥ 5 This study was supported by the Regione Piemonte Ricerca Sanitaria Finalizzata grant 03-08/ACR ASx44, which had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; or preparation, review or approval of the manuscript

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization schedule Baseline characteristics at admission or before randomization did not differ between the 2 groups
Allocation concealment (selection bias)	Low risk	Randomization was conducted centrally using a computer-generated randomization schedule
Blinding (performance bias and detection bias) All outcomes	Low risk	According to the study authors, "a clinician blinded to patient allocation looked at the clinical charts remotely and evaluated the nonobjective components of the CPIS (quality of secretions, chest x-ray, evidence of acute respiratory distress syndrome)." Moreover, all primary outcomes of this review were considered objective, specifically mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis (ITT) was performed by study authors. Withdrawals at 1 year of follow-up: n = 10 (4.78%) in the early tracheostomy group, and n = 4 (1.9%) in the late tracheostomy group
Selective reporting (reporting bias)	Low risk	None was suspected. Clinically relevant outcomes were analysed
Other bias	High risk	No explicit information was provided about the time of follow-up for some postoperative adverse events: stoma inflammation, stoma infection, minor bleeding, major bleeding, pneumothorax, subcutaneous emphysema, tracheo-oesophageal fistula.

Trouillet 2011

Methods	Study design: parallel randomized controlled trial with sample size selected to demonstrate that early tracheostomy achieved an absolute increase in ventilator-free days over 7 days, with 80% power and 5% type I error; 198 participants were required Locale/Setting: Institut de Cardiologie, Hôpital de la Pitié–Salpêtriére, Assistance Publique Hôpitaux de Paris, Université Pierre et Marie Curie, Institut National de la Santé et de la Recherche Médicale, Paris, France

Trouillet 2011 *(Continued)*

	Support: French Ministry of Health
Participants	1. N = 216 (early tracheostomy, n = 109/late tracheostomy, n = 107) 2. Mean age, years: 65 3. Gender: male, 66% (n = 143) 4. Mean Glasgow Coma Scale score: 11.15 5. Mechanically ventilated for acute respiratory failure for 24 hours 6. Simplified Acute Physiology Score II between 35 and 65 7. Participants who had undergone cardiac surgery 8. Still on mechanical ventilation 4 days thereafter 9. Had not successfully passed a mechanical ventilation weaning screening test or a spontaneous breathing trial on the day of randomization, according to the Ely protocol (Ely 1996) 10. Expected to require mechanical ventilation for 7 or more days, according to Trouillet 2009
Interventions	1. Early tracheostomy (before the end of calendar day 5 after surgery) 2. Prolonged intubation with tracheostomy only when mechanical ventilation exceeded day 15 after randomization
Outcomes	1. Ventilator-free days during 1 to 60 days 2. Ventilator-free days during 1 to 28 days 3. Ventilator-free days during 1 to 90 days 4. Mortality at 28 days, 60 days, 90 days 5. Length of ICU stay 6. Length of hospital stay 7. Days of MV during 1 to 60 days 8. Endotracheal prosthesis-free days during 1 to 60 days 9. Participants with unscheduled extubation or decannulation during 1 to 60 days 10. Participants with reintubation or recannulation during 1 to 60 days 11. Participants with non-invasive ventilation > 4 hours/d during 1 to 60 days **Sedation** 1. Duration of intravenous sedation 2. Sedation-free days during 1 to 28 days 3. Cumulative sufentanil dose during 1 to 15 days, µg/kg 4. Cumulative propofol dose during 1 to 15 days, mg/kg 5. Cumulative midazolam dose during 1 to 15 days, mg/kg 6. Days (during 1 to 15 days) of haloperidol therapy 7. Cumulative haloperidol dose during 1 to 15 days, mg/kg 8. VAP after randomization 9. Sternal wound infection 10. Bloodstream infection 11. Days (during 1 to 15 days) nurse-assessed as comfortable (SD) 12. Days (during 1 to 15 days) nurse-assessed as easy management 13. Received oral nutrition at 15 days 14. Bed-to-chair transfer at 15 days 15. Muscle strength assessment 16. Basic Activities of Daily Living Scale score

Trouillet 2011 *(Continued)*

17.Basic Activities of Daily Living Scale score < 6
18.Instrumental Activities of Daily Living Scale score
19.Instrumental Activities of Daily Living Scale score < 8

Mean SF-36 domains

1. Physical functioning
2. Role physical
3. Bodily pain
4. General health
5. Vitality
6. Social functioning
7. Role—emotional
8. Mental health

Mean SF-36 component score (SD)

1. Physical/Mental
2. Mean Hospital Anxiety and Depression Scale score
3. Mean Hospital Anxiety and Depression Subscale A score
4. Mean Hospital Anxiety and Depression Subscale D score
5. Hospital Anxiety and Depression Subscale A score ≥ 8
6. Hospital Anxiety and Depression Subscale D score ≥ 8
7. Mean Impact of Event Scale score
8. Impact of Event Scale score ≥ 30

Notes	Funding: French Ministry of Health. The study sponsor did not participate in the study design, data collection, data analysis, data interpretation or writing or the decision to submit this manuscript for publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization sequence in a 1:1 ratio. Randomization was stratified (minimization) by the Simplified Acute Physiology Score II (either ≤ 45 or > 45) calculated on the day of randomization
Allocation concealment (selection bias)	Low risk	Independent randomization (Unité de Recherche Clinique, Pitié-Salpêtrière Hospital, Paris, France) with password protected and accessed by the principal investigators or the study coordinator after the participant had met selection criteria and the surrogate gave consent. The participant's initials were entered, and treatment allocation was assigned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information was provided on whether data collectors were independent from the researchers who designed the study or were blinded to the allocations. However, all primary outcomes of this review were considered objective, specifically mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomly assigned participants were included in the analyses according to their randomized treatment assignment, all participants received the allocated intervention and none was lost to follow-up during the first 90 days. Participants randomly assigned to the prolonged intubation group who had late tracheostomy were always analysed in the prolonged intubation group
Selective reporting (reporting bias)	Low risk	None suspected. Clinically relevant outcomes were analysed

Trouillet 2011 *(Continued)*

Other bias	Low risk	None suspected

Young 2013

Methods	Study design: parallel randomized controlled trial with sample size of 899 participants available for analysis of the primary outcome based on the power to detect an 8.3% absolute change in 30-day mortality from the "late" group value of 31.5% with 80% power and a 5% level of significance. Study authors carried out the intention-to-treat analysis Locale/Setting: 70 adult general and 2 cardiothoracic critical care units in 13 university and 59 non-university hospitals in the United Kingdom: Bedford Hospital; Castle Hill Hospital; Causeway Hospital; Chorley Hospital; City General Hospital Stoke on Trent; City Hospital Birmingham; Derriford Hospital; Dumfries & Galloway Royal Infirmary; Eastbourne District General Hospital; Freeman Hospital; Glan Clwyd District General Hospital; Glenfield Hospital; Hairmyres Hospital; Huddersfield Royal Infirmary Hall; James Cook University Hospital; James Paget Hospital; John Radcliffe Hospital; King's College Hospital; King George Hospital; Kings Mill Hospital; Kingston Hospital; Leeds General Infirmary; Leicester Royal Infirmary; Luton & Dunstable Hospital; Manchester Royal Infirmary; Medway Maritime Hospital; Newcastle General Hospital; New Cross Hospital; Ninewells Hospital; North Middlesex Hospital; Peterborough District Hospital Support: University of Oxford, UK Intensive Care Society and the Medical Research Council
Participants	1. N = 909 (early tracheostomy, n = 455/late tracheostomy, n = 454) 2. Mechanically ventilated patients in adult critical care units, who were identified by the treating clinician in the first 4 days after admission as likely to require at least 7 more days of ventilatory support 3. Mean age, years: 63.9 4. Gender: male, 58.6% (n = 527) 5. APACHE II: 19.8 6. Medical admissions: 79.2% (n = 712) 7. Surgical admissions: 20.8% (n = 187)
Interventions	1. Early tracheostomy: within 4 days of mechanical ventilation 2. Late tracheostomy: after 10 days of mechanical ventilation Tracheostomies were performed according to each critical care unit's local practice (percutaneous or surgical tracheostomy). All other care was provided at the discretion of the treating clinicians
Outcomes	1. Mortality at 30 days 2. Mortality until ICU discharge 3. Mortality until hospital discharge 4. Mortality at 1 year of follow-up 5. Mortality at 2 years of follow-up 6. Antibiotic use to 30 days (antibiotic median free days at 30 days of follow-up)
Notes	This study was supported by the University of Oxford, the UK Intensive Care Society and the Medical Research Council,.which had no influence on the design and conduct of the study; the collection, management, analysis and interpretation of the data; or preparation, review or approval of the manuscript. The randomization service was provided by the Health Services Research Unit at the University of Aberdeen

Risk of bias

Bias	Authors' judgement	Support for judgement

Young 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomization was conducted using an automated 24-hour telephone service based on an algorithm that minimized the imbalance between groups in the study by allocating each participant, with 80% probability, to the group that minimized the imbalance in the following co-variates: centre, age, sex and 7 major diagnostic groups (intracranial pathology, altered consciousness due to drug or metabolic causes, acute peripheral nerve or muscle disorder, pulmonary pathology, burns, heart failure and other)
Allocation concealment (selection bias)	Low risk	Randomization was conducted using an automated 24-hour telephone service
Blinding (performance bias and detection bias) All outcomes	Low risk	Treatment assignment could not be blinded to the caring team nor to the analysis team because it was apparent from the data to which group a participant had been assigned. All primary outcomes of this review were considered objective, specifically mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow of participants was clearly reported and study authors carried out intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	None was suspected. Study authors valuated relevant outcomes
Other bias	Low risk	None was suspected

Zheng 2012

Methods	Study design: parallel randomized controlled trial without sample size calculation Locale/Setting: Department of Surgical Intensive Care Unit, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China Support: Scientific Research Fund for Capital Medicine Development
Participants	1. N = 119 (early tracheostomy, n = 58/late tracheostomy, n = 61) 2. Mean age, years: 67.7 3. Gender: male, 62.2% (n = 74) 4. APACHE II: 19.56 5. Mechanically ventilated for acute respiratory failure 6. PaO_2/FiO_2 (fraction of inspired oxygen) less than or equal to 200 mm Hg 7. Acute Physiology and Chronic Health Evaluation score II (APACHE II): 8 more than 15 8. Sequential organ failure assessment (SOFA) 9, score equal to or greater than 5 9. Without pulmonary infection, estimated by a modified clinical pulmonary infection score (CPIS) of 10 more than 6 10. Estimated to require MV greater than 14 days by the 2 attending physicians
Interventions	1. Early percutaneous dilatational tracheostomy (PDT) on day 3 of MV and ventilated continuously after that 2. Late PDT group was continuously ventilated via endotracheal intubation and was tracheostomized with PDT on day 15 of MV if they still needed MV PDT performed according to Griggs 1991
Outcomes	1. Ventilator-free days (at day 28 after randomization) 2. Sedation-free days (at day 28 after randomization)

Zheng 2012 *(Continued)*

	3. ICU-free days (at day 28 after randomization) 4. Successful weaning (at day 28 after randomization) 5. Intensive care unit discharge (at day 28 after randomization) 6. Ventilator-associated pneumonia incidence (at day 28 after randomization) 7. 28-day and 60-day mortality 8. Complications associated with PDT during the 28 days after randomization
Notes	1. Intraoperative complications were defined as minor bleeding (bleeding less than 100 mL), significant bleeding (any bleeding event that required blood transfusions), difficult tracheostomy tube placement (requiring at least 2 attempts for insertion during primary placement procedure), hypoxaemia (SpO_2 < 90% for longer than 90 seconds), arrhythmia and cardiac arrest 2. Postoperative complications: stoma inflammation, minor bleeding, significant bleeding, pneumothorax, subcutaneous emphysema, tracheo-oesophageal fistula, cannula displacement or need for cannula replacement This study was supported by a grant from the Scientific Research Fund for Capital Medicine Development

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignments were generated by computer
Allocation concealment (selection bias)	Low risk	Random assignments were concealed in sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant assignment was known only by study investigators. All participants were treated according to the same management procedures; therefore, the effects of management heterogeneity on study results were limited. However, no clear mention was made of independence of data collectors for any outcome. However, all primary outcomes of this review were considered objective, specifically mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomly assigned participants were analysed
Selective reporting (reporting bias)	Low risk	None was suspected. Clinically relevant outcomes were analysed
Other bias	Low risk	None was suspected

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

Study	Reason for exclusion
Blot 2008	Early tracheotomy vs prolonged endotracheal intubation. No data available for participants subjected to late tracheostomy
Bouderka 2004	Early tracheostomy vs prolonged endotracheal intubation
El-Naggar 1976	Early tracheostomy vs prolonged endotracheal intubation

Study	Reason for exclusion
Fayed 2012	Early tracheostomy vs prolonged endotracheal intubation
Koch 2012	Late tracheostomy ≥ 6 days after intubation (before 10 days)
Rodriguez 1990	Late tracheostomy > 8 days after admission (before 10 days)
Saffle 2002	Early tracheostomy vs continued endotracheal intubation with no data available specifically for participants subjected to late tracheostomy
Stauffer 1981	Early tracheostomy vs continued endotracheal intubation
Sugerman 1997	Early tracheostomy vs continued endotracheal intubation with no data available for participants subjected to late tracheostomy

Characteristics of studies awaiting assessment *[ordered by study ID]*

Dunham 2014

Methods	Parallel randomized controlled trial
Participants	Participants with severe traumatic brain injury
Interventions	Early vs late tracheostomy
Outcomes	Ventilator-associated pneumonia rates, ventilator days, hospital mortality rates
Notes	None

Mohamed 2014

Methods	Parallel randomized controlled trial
Participants	Participants mechanically ventilated for respiratory failure > 24 hours
Interventions	Early and late percutaneous dilatational tracheostomy
Outcomes	Mechanical ventilation duration (MVD), length of ICU stay, length of hospital stay, incidence of ventilator-associated pneumonia
Notes	

Priyamvadha 2012

Methods	Parallel randomized controlled trial
Participants	No data available
Interventions	No data available

Priyamvadha 2012 *(Continued)*

Outcomes	No data available
Notes	The article was not acquired in full, and no study author contact was found on the Web

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

Dumire 2008

Trial name or title	A prospective, randomized trial of early versus conventional conversion from endotracheal intubation to percutaneous tracheostomy for ventilatory support of trauma patients with severe brain injury
Methods	Open-label parallel randomized controlled trial
Participants	1. 18 years of age or older 2.- TBI defined as penetrating or blunt brain injury including a. Subarachnoid haemorrhage b.Subdural haemorrhage c.Epidural haemorrhage d.Brain contusion e.Diffuse axonal injury 3. Mechanically ventilated by endotracheal intubation 4. Projected to need ventilation support for longer than 14 days according to the following: GCS measured in field less than or equal to 8 and GCS on day 3 that remains less than or equal to 8 5. Informed consent obtained from participant or legal representative
Interventions	1. Early tracheostomy (less than or equal to 72 hours) 2. Late tracheostomy (10 to 14 days)
Outcomes	1. Total number of mechanical ventilation days until discharge 2. Total number of hospital days until discharge 3. Incidence of ventilator-associated pneumonia until discharge 4. Incidence of accidental extubation until discharge 5. Incidence of death until discharge
Starting date	February 2006
Contact information	Pennsylvania, United States Memorial Medical Center Johnstown Pennsylvania 15905
Notes	

Huttner 2010

Trial name or title	WEANING study: "Weaning by early versus late tracheostomy in supratentorIal intracerebral bleedings"
Methods	Open-label parallel randomized controlled trial
Participants	1. Participants requiring intubation/mechanical ventilation 2. Supratentorial intracerebral haemorrhage including a. Primary spontaneous ICH (lobar/deep) b. ICH related to anticoagulant therapy - with or without intraventricular haemorrhage - with or without occlusive and/or communicating hydrocephalus 3. Haematoma volume > 0 mL and < 60 mL 4. Age 18 to 85 years 5. Informed consent (legal representative)
Interventions	1. "Early" tracheostomy within 72 hours after hospital admission 2. "Late" tracheostomy (control group; undergoing conventional tracheostomy between day 12 and day 14 if extubation fails). Both groups received plastic tracheostomy
Outcomes	1. Cumulative time requiring mechanical ventilation and overall duration of neurocritical care 30 days 2. Incidence of respirator-associated pneumonia 30 days 3. Cumulative consumption of sedative drugs 30 days 4. Incidence of episodes with increased intracranial pressure 30 days 5. In-hospital mortality 30 days 6. Three months functional outcome (mRS) 90 days. No functional outcome after 3 months using the modified Rankin Scale
Starting date	July 2010
Contact information	Hagen B. Huttner, MD tel: +4991318544523 hagen.huttner@uk-erlangen.de
Notes	

Kluge 2009

Trial name or title	Early versus late percutaneous dilation tracheostomy in mechanically ventilated patients with chronic obstructive pulmonary disease
Methods	Open-label parallel randomized controlled trial
Participants	1. >18 years old 2. Diagnosis of COPD (GOLD stage III or IV) 3. Suspected long-time invasive mechanical ventilation due to ARF (> 10 days)

Kluge 2009 *(Continued)*

	4. Informed consent of participant or legal guardian
Interventions	Early tracheostomy: tracheostomy at the next possible opportunity but not later than 72 hours after initiation of invasive ventilation Participants in the control group will be invasively ventilated at least until day 10
Outcomes	1. Cumulative duration of mechanical ventilation (in days) days 1 to 28 2. All-cause mortality days 28 and 90 and end of ICU stay 3. Length of stay on ICU/hospital end of ICU/hospital stay 4. Infections (ventilator-associated pneumonia, spectrum of pathogens in BALF, infectious complications) days 1 to 28 5. Cumulative use of sedatives days 1 to 28 6. Quality of life discharge from ICU days 28 and 90
Starting date	October 2009
Contact information	Stefan Kluge, MD tel: +4940 7410 ext 57010 s.kluge@uke.de
Notes	

Ranieri 2009

Trial name or title	Efficacy of early tracheostomy to reduce incidence of ventilator acquired pneumonia (VAP)
Methods	Open-label parallel randomized controlled trial
Participants	1. Oro/nasotracheal intubation for less than 3 days 2. Simplified Acute Physiology Score (SAPS II) between 35 and 65 upon admission to intensive care unit (ICU)
Interventions	1. Early tracheostomy on days 3 to 5 2. Late tracheostomy on days 10 to 12
Outcomes	1. Increase in "ventilator-associated pneumonia-free days." Follow-up terminates on day 28 from the date of oro/nasotracheal intubation 2. Increase in "ventilator-free days." Follow-up terminates on day 28 from the date of oro/nasotracheal intubation 3. Reduction in mortality at 1 year
Starting date	June 2004
Contact information	Italy University of Turin, Department of Anesthesia and Intensive Care Medicine Turin 10126
Notes	

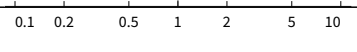
DATA AND ANALYSES

Comparison 1. Early vs late tracheostomy

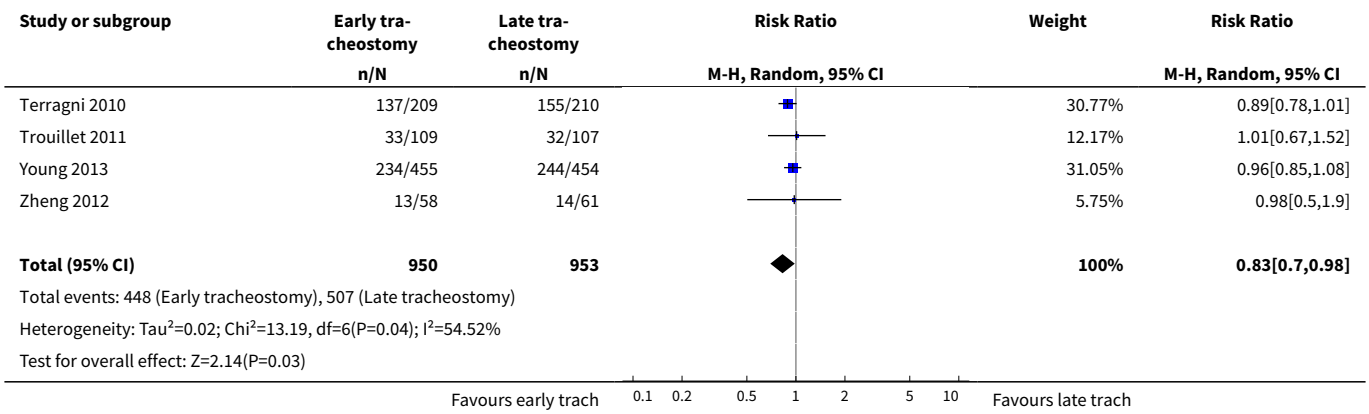
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at longest follow-up time available in studies	7	1903	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]
2 Mortality at 28 days	3	744	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.64, 1.08]
3 Mortality at 30 days	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Mortality at 60 days	2	335	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.65, 1.35]
5 Mortality at 1 year	2	1318	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.82, 0.99]
6 Mortality until ICU discharge	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Ventilator-free days during 1 to 28 days	2	335	Mean Difference (IV, Random, 95% CI)	1.62 [-0.01, 3.25]
8 Days of MV during 1 to 60 days	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
9 Length of ICU stay	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
10 ICU discharge (at day 28 after randomization)	2	538	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.08, 1.55]
11 Pneumonia	5		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12 Sternal wound infection	2	480	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.57, 1.76]

Analysis 1.1. Comparison 1 Early vs late tracheostomy, Outcome 1 Mortality at longest follow-up time available in studies.

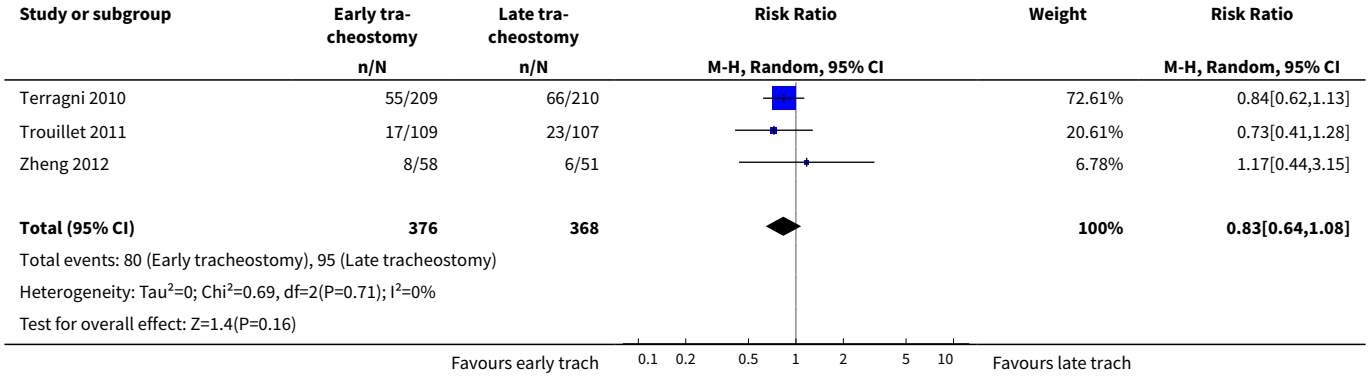
Study or subgroup	Early tracheostomy n/N	Late tracheostomy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Barquist 2006	2/29	5/31		1.19%	0.43[0.09,2.03]
Bösel 2013	10/30	20/30		7.48%	0.5[0.28,0.88]
Rumbak 2004	19/60	37/60		11.58%	0.51[0.34,0.78]



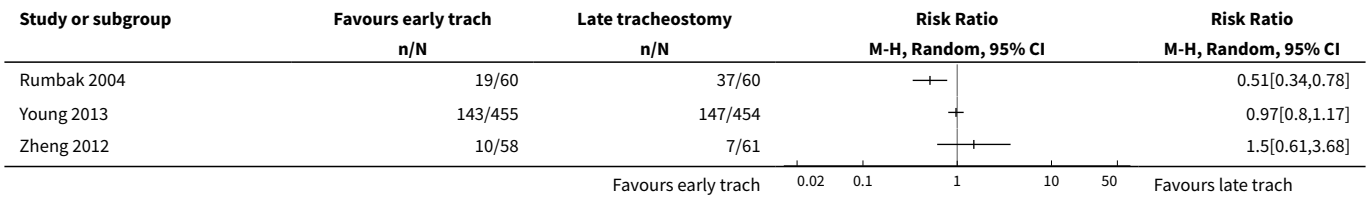
Favours early trach
Favours late trach



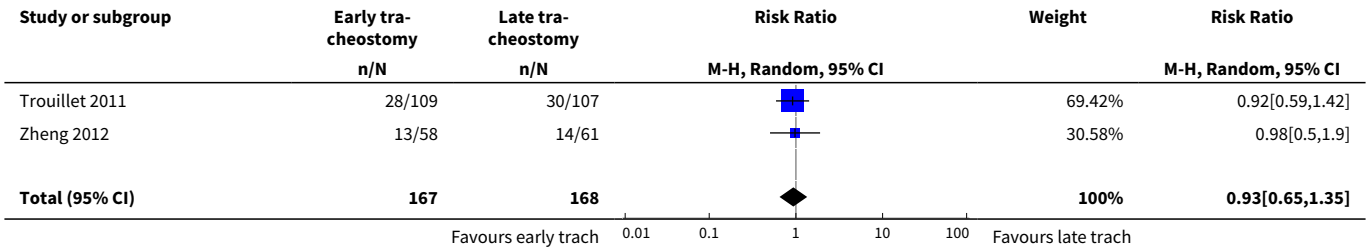
Analysis 1.2. Comparison 1 Early vs late tracheostomy, Outcome 2 Mortality at 28 days.

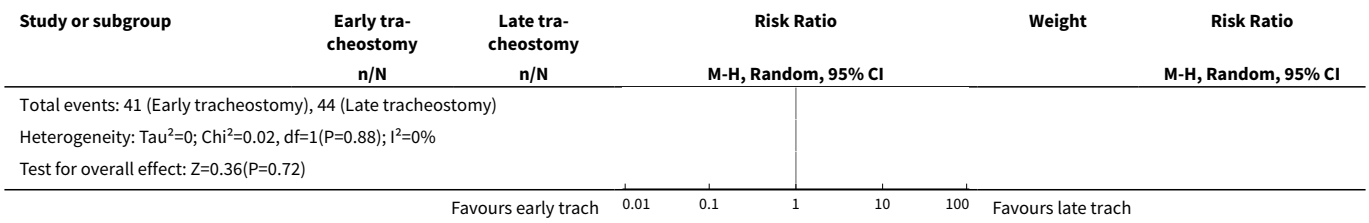


Analysis 1.3. Comparison 1 Early vs late tracheostomy, Outcome 3 Mortality at 30 days.

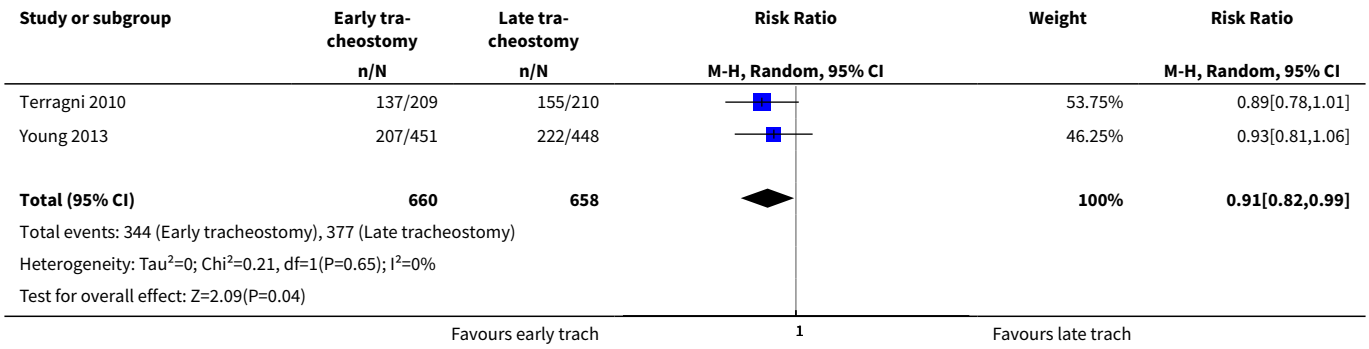


Analysis 1.4. Comparison 1 Early vs late tracheostomy, Outcome 4 Mortality at 60 days.

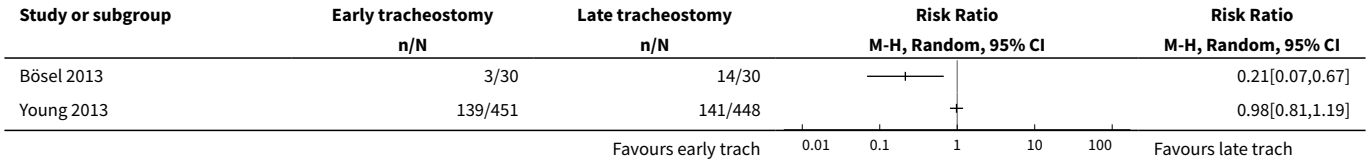




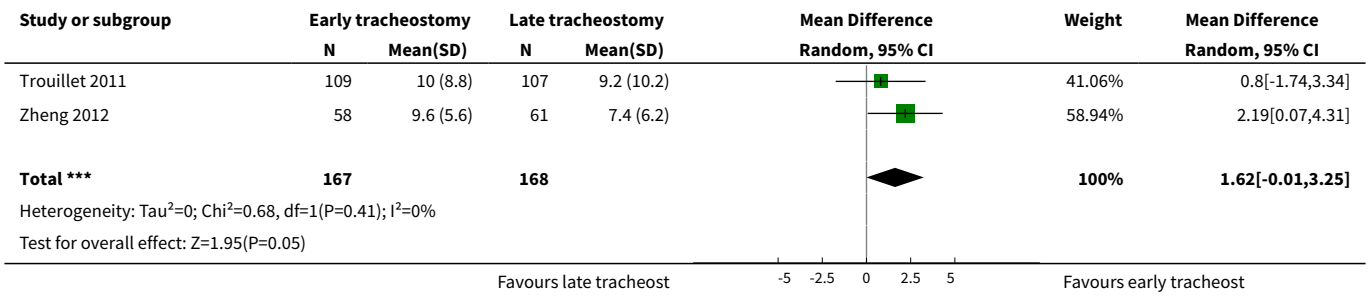
Analysis 1.5. Comparison 1 Early vs late tracheostomy, Outcome 5 Mortality at 1 year.



Analysis 1.6. Comparison 1 Early vs late tracheostomy, Outcome 6 Mortality until ICU discharge.



Analysis 1.7. Comparison 1 Early vs late tracheostomy, Outcome 7 Ventilator-free days during 1 to 28 days.

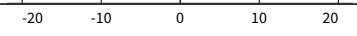


Analysis 1.8. Comparison 1 Early vs late tracheostomy, Outcome 8 Days of MV during 1 to 60 days.

Study or subgroup	Early tracheostomy		Late tracheostomy		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Rumbak 2004	60	7.6 (4)	60	17.4 (5.3)		-9.8[-11.48,-8.12]
Trouillet 2011	109	17.9 (14.9)	107	19.3 (16.9)		-1.4[-5.65,2.85]

Analysis 1.9. Comparison 1 Early vs late tracheostomy, Outcome 9 Length of ICU stay.

Study or subgroup	Favours early tracheost		Late tracheostomy		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Trouillet 2011	109	23.9 (21.3)	107	25.5 (22.2)		-1.6[-7.4,4.2]
Rumbak 2004	60	4.8 (1.4)	60	16.2 (3.8)		-11.4[-12.42,-10.38]

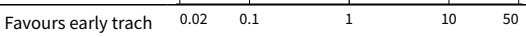


Analysis 1.10. Comparison 1 Early vs late tracheostomy, Outcome 10 ICU discharge (at day 28 after randomization).

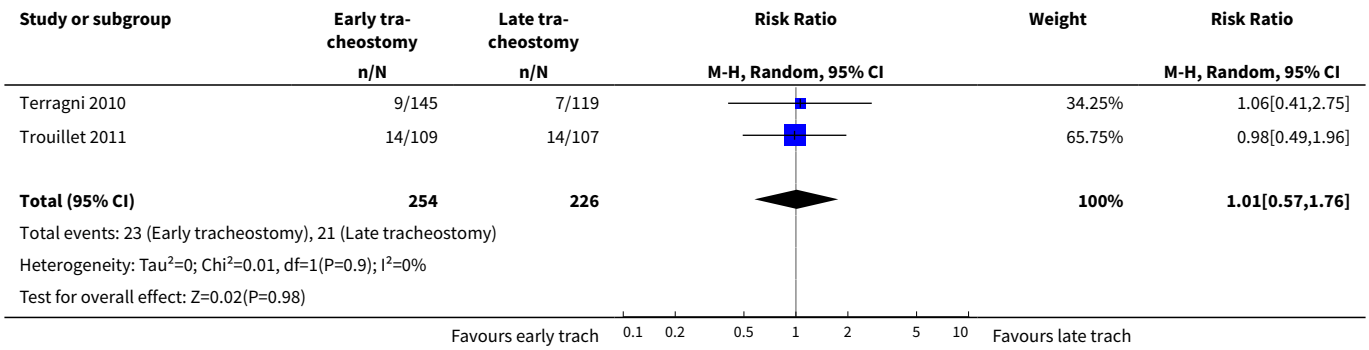
Study or subgroup	Early tracheostomy	Late tracheostomy	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Terragni 2010	101/209	82/210		67.85%	1.24[0.99,1.54]
Zheng 2012	39/58	29/61		32.15%	1.41[1.03,1.95]
Total (95% CI)	**267**	**271**		**100%**	**1.29[1.08,1.55]**
Total events: 140 (Early tracheostomy), 111 (Late tracheostomy)					
Heterogeneity: Tau^2=0; Chi^2=0.46, df=1(P=0.5); I^2=0%					
Test for overall effect: Z=2.78(P=0.01)					

Analysis 1.11. Comparison 1 Early vs late tracheostomy, Outcome 11 Pneumonia.

Study or subgroup	Early tracheostomy	Late tracheostomy	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Dunham 1984	20/34	20/40		1.18[0.77,1.79]
Rumbak 2004	3/60	15/60		0.2[0.06,0.66]
Terragni 2010	30/209	44/210		0.69[0.45,1.05]
Trouillet 2011	50/109	47/107		1.04[0.78,1.4]
Zheng 2012	17/58	30/61		0.6[0.37,0.96]



Analysis 1.12. Comparison 1 Early vs late tracheostomy, Outcome 12 Sternal wound infection.



ADDITIONAL TABLES

Table 1. Continuous and dichotomous outcomes not possible to be combined in a meta-analysis

1. Primary outcomes	n	Estimate effect (MD or RR, 95% CI, P, NNTB, 95% CI for NNTB)	Favoured group	Study
1.1. Mortality				
1.1.1. Mortality at 30 days	120	RR 0.51 (0.34 to 0.78, P value 0.002, NNTB = 3.3)	Early tracheostomy	Rumbak 2004
1.1.2. Mortality at 30 days	909	RR 0.97 (0.80 to 1.17, P value 0.76)	Early tracheostomy	Young 2013
1.1.3. Mortality at 30 days	119	RR 1.50 (0.61 to 3.68, P value 0.37)	Late tracheostomy	Zheng 2012
1.1.4. Mortality at 90 days	216	RR 1.01 (0.67 to 1.52, P value 0.95)	Late tracheostomy	Trouillet 2011
1.1.5. Mortality at 180 days	60	RR 0.44 (0.23 to 0.85, P value 0.01, NNTB = 2.8)	Early tracheostomy	Bösel 2013
1.1.6. Mortality at 2 years	909	RR 0.94 (0.83 to 1.06, P value 0.33)	Early tracheostomy	Young 2013
1.1.7. Mortality until ICU discharge	60	RR 0.21 (0.07 to 0.67, P value 0.008, NNTB = 2.7)	Early tracheostomy	Bösel 2013
1.1.8. Mortality until ICU discharge	909	RR 0.98 (0.81 to 1.19, P value 0.83)	Early tracheostomy	Young 2013
1.1.9. Mortality until hospital discharge	909	0.96 (0.82 to 1.12, P value 0.58)	Early tracheostomy	Young 2013
1.2. Duration of artificial ventilation				
1.2.1. Days of mechanical ventilation 1 to 60 days	120	MD -9.80 (-11.48 to -8.12, P value < 0.001)	Early tracheostomy	Rumbak 2004

Table 1. Continuous and dichotomous outcomes not possible to be combined in a meta-analysis *(Continued)*

1.2.2. Days of mechanical ventilation 1 to 60 days	216	MD -1.40 (-5.65 to 2.85, P value 0.52)	Early tracheostomy	Trouillet 2011
1.2.3. Ventilator-free days during 1 to 60 days	216	MD 2.10 (-4.05 to 8.25, P value 0.50)	Early tracheostomy	Trouillet 2011
1.2.4. Ventilator-free days during 1 to 90 days	216	MD 1.80 (-7.94 to 11.54, P value 0.72)	Early tracheostomy	Trouillet 2011
1.2.5. Intubation for longer than 21 days	74	RR 0.85 (0.53 to 1.36, P value 0.49)	Late tracheostomy	Dunham 1984
2. Secondary outcomes	**n**	**Estimate effect (MD or RR, 95% CI, P, NNTH, 95% CI for NNTH)**	**Favoured group**	**Study**
2.1. Length of stay in ICU				
2.1.1. Time spent on ICU (days)	120	MD -11.40 (-12.42 to -10.38, P value < 0.001)	Early tracheostomy	Rumbak 2004
2.1.2. Time spent on ICU (days)	419	-1.40 (-5.65 to 2.85, P value 0.52)	Early tracheostomy	Trouillet 2011
2.2. Ventilator-associated pneumonia				
2.2.1. Ventilator-associated pneumonia	74	RR 1.18 (0.77 to 1.79, P value 0.45)	Late tracheostomy	Dunham 1984
2.2.2. Ventilator-associated pneumonia	120	RR 0.20 (0.06 to 0.66, P value 0.008, NNTB = 1.66)	Early tracheostomy	Rumbak 2004
2.2.3. Ventilator-associated pneumonia	419	RR 0.69 (0.45 to 1.05, P value 0.08)	Early tracheostomy	Terragni 2010
2.2.4. Ventilator-associated pneumonia	216	RR 1.04 (0.78 to 1.40, P value 0.77)	Late tracheostomy	Trouillet 2011
2.2.5. Ventilator-associated pneumonia	119	RR 0.60 (0.37 to 0.96, P value 0.03, NNTB = 5)	Early tracheostomy	Zheng 2012
2.3. Laryngotracheal lesions				
2.3.1. Stoma inflammation	264	RR 1.00 (0.57 to 1.78, P value 0.99)	Late tracheostomy	Terragni 2010
2.3.2. Stoma infection	264	RR 1.06 (0.41 to 2.75, P value 0.91)	Late tracheostomy	Terragni 2010
2.3.3. Postoperative minor bleeding	264	RR 1.09 (0.39 to 3.07, P value 0.86)	Late tracheostomy	Terragni 2010
2.3.4. Postoperative major bleeding	264	RR 0.82 (0.17 to 3.99, P value 0.81)	Early tracheostomy	Terragni 2010
2.3.5. Postoperative bleeding	60	RR 0.03 (0.00 to 0.55, P value 0.02, NNTB = 2.12)	Early tracheostomy	Bösel 2013

Table 1. Continuous and dichotomous outcomes not possible to be combined in a meta-analysis *(Continued)*

2.3.6. Intraoperative minor bleeding	264	RR 0.55 (0.09 to 3.22, P value 0.50)	Early tracheostomy	Terragni 2010
2.3.7. Intraoperative significant bleeding	264	No event in both groups	-	Terragni 2010
2.3.8. Tracheo-oesophageal fistula	264	RR 2.47 (0.10 to 59.98, P value 0.58)	Late tracheostomy	Terragni 2010
2.3.9. Significant laryngotracheal pathology	74	RR 1.41 (0.47 to 4.22, P value 0.54)	Late tracheostomy	Dunham 1984
2.3.10. Tracheal stenosis (%) 0 to 20 (in-hospital)	120	RR 1.27 (1.04 to 1.55, P value 0.02, NNTH=10)	Late tracheostomy	Rumbak 2004
2.3.11. Tracheal stenosis (%) 21 to 50 (in-hospital)	120	RR 0.50 (0.20 to 1.25, P value 0.14)	Early tracheostomy	Rumbak 2004
2.3.12. Tracheal stenosis (%) > 50 (in-hospital)	120	RR 0.40 (0.08 to 1.98, P value 0.26)	Early tracheostomy	Rumbak 2004
2.3.13. Tracheal stenosis irrespective of severity (in-hospital)	120	RR 1.03 (0.98 to 1.09, P value 0.24)	Late tracheostomy	Rumbak 2004
2.3.14. Tracheal stenosis (%) 0 to 20 (10-week post intubation)	120	RR 2.00 (1.14 to 3.51, P value 0.02, NNTH = 4.54)	Late tracheostomy	Rumbak 2004
2.3.15. Tracheal stenosis (%) 21 to 50 (10-week post intubation)	120	RR 1.67 (0.65 to 4.30, P value 0.29)	Late tracheostomy	Rumbak 2004
2.3.16. Tracheal stenosis (%) > 50 (10-week post intubation)	120	RR 1.25 (0.35 to 4.43, P value 0.73)	Late tracheostomy	Rumbak 2004
2.3.17. Tracheal stenosis irrespective of severity (10-week post intubation)	120	RR 1.78 (1.24 to 2.57, P value 0.002, NNTH = 3.33)	Late tracheostomy	Rumbak 2004

NNTB: number needed to treat for an additional beneficial outcome
NNTH: number needed to treat for an additional harmful outcome

Table 2. Primary and secondary outcomes expressed as medians

Study ID	Comparison groups	Median	Interquartile range	P value
1. Primary outcome: ventilator free-days (at day 28)				
Terragni 2010	Early tracheostomy	11	0to 21	0.02
	Late tracheostomy	6	0 to 17	
2. Primary outcome: ventilation time (days)				
Bösel 2013	Early tracheostomy	15	10 to 17	0.23
	Late tracheostomy	12	8 to 16	
3. Secondary outcome: intensive care unit-free days (at day 28)				

Table 2. Primary and secondary outcomes expressed as medians *(Continued)*

Terragni 2010	Early tracheostomy	0	0 to 13	0.02
	Late tracheostomy	0	0 to 8	
4. Secondary outcome: intensive care unit length of stay (days)				
Bösel 2013	Early tracheostomy	17	13 to 22	0.38
	Late tracheostomy	18	16 to 28	
5. Secondary outcome: intensive care unit-free days (at day 28)				
Zheng 2012	Early tracheostomy	8.0	5 to 12	0.048
	Late tracheostomy	3.0	0 to 12	

Statistical test referred to in Terragni 2010; Zheng 2012; Bösel 2013: Wilcoxon signed rank test.

APPENDICES

Appendix 1. Glossary of terms

Term	Definition
COPD (chronic obstructive pulmonary disease)	Disease of chronic diffuse irreversible airflow obstruction. Subcategories of COPD include chronic bronchitis and pulmonary emphysema
Critically ill adults	Adults with a disease or in a state in which death is possible or imminent
Early tracheostomy	Although not precisely defined, this usually refers to a tracheostomy performed from 2 days to 10 days after intubation
Late tracheostomy	Although not precisely defined, this usually refers to a tracheostomy performed after 10 days of intubation
Percutaneous tracheostomy	Usually a tracheostomy based on (1) needle-guide wire airway access followed by serial dilations with sequentially larger dilators; (2) guide wire dilating forceps; (3) mini tracheostomy only for emergency airway access or for aspiration of retained bronchopulmonary secretions
Pneumomediastinum or mediastinal emphysema	Presence of air in the mediastinal tissues due to leakage of air from the tracheobronchial tree, usually as a result of trauma
Pneumothorax	Accumulation of air or gas in the pleural space, which may occur spontaneously or as a result of trauma or a pathological process, or may be deliberately introduced
Prolonged mechanical ventilation	At least 21 consecutive days for 6 or more hours per day of any method of artifical breathing that employs mechanical or non-mechanical means to force air into and out of the lungs. Artificial respiration or ventilation is used in individuals who have stopped breathing or have respiratory insufficiency to increase their intake of oxygen (O_2) and excretion of carbon dioxide (CO_2)
Ramsay score (Ramsay 2000)	Numerical scale of responses to verbal, tactile or nociceptive stimuli

(Continued)

Self-extubations	Unplanned removal of an endotracheal airway tube by a patient
Severe hypoxia	Referred to as low oxygen levels or anoxia, this is a relatively common cause of injury to the central nervous system. Prolonged brain anoxia may lead to brain death or to a persistent vegetative state. Histologically, this condition is characterized by neuronal loss, which is most prominent in the hippocampus; globus pallidus; cerebellum; and inferior olives
Surgical tracheostomy	Tracheostomy performed by surgeons in the operating theatre using an open technique
Tracheal aspiration	Aspiration or suctioning of oropharyngeal secretions past tracheal cuffs into the lungs in mechanically ventilated patients (usually in the intensive care unit (ICU))
Ventilator-associated pneumonia	Serious inflammation of the lungs in patients who required the use of a pulmonary ventilator. It is usually caused by cross-bacterial infection in the hospital (nosocomial infection)

Appendix 2. Ovid MEDLINE search strategy

1. exp Tracheostomy/ or tracheo?tom*.af.
2. Respiration, Artificial/ or Laryngeal Masks/ or Positive-Pressure Respiration/ or Pulmonary Ventilation/ or Ventilators, Mechanical/ or High-Frequency Ventilation/ or ((early or precocious or premature) and (late or tardy)).ti,ab. or artificial respiration*.ti,ab. or (ventilat* adj3 (mechanical or high?frequency or oscillation or positive pressure or jet or weaning or pulmonary)).mp. or (respirat* or ventilator*).ti,ab. or chest tube*.ti,ab. or ((airway* or laryngeal) adj3 mask*).mp.
3. (randomized 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. CENTRAL search strategy

#1 MeSH descriptor: [Tracheostomy] explode all trees
#2 tracheo?tom*
#3 #1 or #2
#4 MeSH descriptor: [Respiration, Artificial] explode all trees
#5 MeSH descriptor: [Laryngeal Masks] explode all trees
#6 MeSH descriptor: [Positive-Pressure Respiration] explode all trees
#7 MeSH descriptor: [Pulmonary Ventilation] explode all trees
#8 MeSH descriptor: [Ventilators, Mechanical] explode all trees
#9 MeSH descriptor: [High-Frequency Ventilation] explode all trees
#10 ((early or precocious or premature) and (late or tardy)):ti,ab or (artificial respiration*):ti,ab or (ventilat* near (mechanical or high?frequency or oscillation or (positive pressure) or jet or weaning or pulmonary)):ti,ab or (respirat* or ventilator*):ti,ab or (chest tube*):ti,ab or ((airway* or laryngeal) near mask*)
#11 #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 #3 and #11

Appendix 4. Ovid EMBASE search strategy

1. exp tracheostomy/ or tracheo?tom*.af.
2. artificial ventilation/ or laryngeal mask/ or positive end expiratory pressure/ or lung ventilation/ or mechanical ventilator/ or high frequency ventilation/ or ((early or precocious or premature) and (late or tardy)).ti,ab. or artificial respiration*.ti,ab. or (ventilat* adj3 (mechanical or high?frequency or oscillation or positive pressure or jet or weaning or pulmonary)).mp. or (respirat* or ventilator*).ti,ab. or chest tube*.ti,ab. or ((airway* or laryngeal) adj3 mask*).mp.
3. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab. 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

Appendix 5. LILACS search strategy

(Tracheostomy OR Traqueostomia OR Tracheostomies OR Traqueostomias OR Tracheotomy OR Tracheotomies) AND (((early or precocious) and (late)) OR (Artificial Respiration) OR (Artificial Respirations) OR (Ventilation, Mechanical) OR (Mechanical Ventilation) OR (Mechanical Ventilations) OR (High-Frequency-Ventilation) OR (High-Frequency Ventilations) OR (High Frequency Ventilation) OR (High Frequency Ventilations) OR (High-Frequency Oscillation Ventilation) OR (High-Frequency Oscillation Ventilations) OR (High Frequency Oscillation

Ventilation) OR (High-Frequency Positive Pressure Ventilation) OR (High Frequency Positive Pressure Ventilation) OR (High-Frequency Jet Ventilation) OR (High-Frequency Jet Ventilations) OR (High Frequency Jet Ventilation) OR (Ventilator-Weaning) OR (Ventilator Weaning) OR (Respirator Weaning) OR (Mechanical Ventilator Weaning) OR (Mechanical Ventilator) OR (Mechanical Ventilators) OR (Pulmonary Ventilators) OR (Pulmonary Ventilator) OR (Respirators) OR (Respirator) OR (Ventilators) OR (Ventilator) OR (Artificial Respiration) OR (Artificial Respirations) OR (Mechanical Ventilation) OR (Mechanical Ventilations) OR (Chest Tubes) OR (Chest Tubes) OR (Chest Tube) OR (Laryngeal Masks) OR (Laryngeal Mask) OR (Laryngeal Mask Airway) OR (Laryngeal Mask Airways) OR (Mechanical Ventilator) OR (Mechanical Ventilators) OR (Pulmonary Ventilators) OR (Pulmonary Ventilator) OR (Respirators) OR (Respirator) OR (Ventilators) OR (Ventilator))

Appendix 6. Current Controlled Trials search strategy

(tracheostomy or tracheostomies) and (timing or ((early or precocious) and (late or later)))

Appendix 7. PEDro search strategy

tracheostomy or tracheostomies

Appendix 8. CINAHL search strategy

(Tracheostomy OR Tracheostomies) and (early and late)

Appendix 9. Extraction sheet

Early versus late tracheostomy for critically ill patients

Study ID: **Date of study (year):** **Review ID:**

Reviewer:

Author (last name):

Locale of study:

I. ACTION

Contact author for:

II. PARTICIPANTS

Participants

a. N:

b. Age (mean), years:

c. Diagnosis (e.g. burning, lung disease):

d. Method to characterize patients as 'critically ill'

e. Method to predict prolonged artificial ventilation:

f. Gender:

g. Setting:

h. Statistical differences at baseline:

III. INTERVENTIONS

Early tracheostomy:

Timing of tracheotomies (days (e.g. from day 0 of mechanical ventilation)):

Type of tracheostomy (e.g. percutaneous or surgical tracheostomy)

Late tracheostomy:

Timing of tracheotomies (days (e.g. from day 0 of mechanical ventilation)):

Type of tracheostomy (e.g. percutaneous or surgical tracheostomy)

IV. OUTCOMES

(final or change from baseline values)

Primary outcomes

1. Mortality (time to mortality or frequency at any time point: in hospital, in ICU, after discharge)

2. Duration of artificial ventilation

Secondary outcomes

1. Length of stay in the ICU (or frequency at any time point)

2. Ventilator-associated pneumonia at any time point

3. Laryngotracheal lesions at any time point (in epiglottis, vocal cord, larynx, subglottic ulceration and inflammation)

4. Eating/vocal/speech problems

V. METHODOLOGICAL QUALITY OF STUDY

Please mark the appropriate item.

Was the random allocation sequence adequately generated?

Low risk:

High risk:

Unclear risk:

Was allocation adequately concealed?

Low risk:

High risk:

Unclear risk:

Blinding: Was knowledge of the allocated interventions adequately prevented during the study?

Low risk:

High risk:

Unclear risk:

Were incomplete outcome data adequately addressed?

Low risk:

High risk:

Unclear risk:

Are reports of the study free of the suggestion of selective reporting?

Low risk:

High risk:

Unclear risk:

Other bias?

Low risk:

High risk:

Unclear risk:

VI. Observation (including non-published data)

Appendix 10. Other potentially relevant outcomes not planned in the protocol of this systematic review

Outcome	n	Estimate effect (MD or RR, 95% CI, P, NNTB, 95% CI for NNTB)	Favoured group	Study
1. Length of hospital stay (days)	216	RR 1.50 (-5.69 to 8.69, P value 0.68)	Late tracheostomy	Trouillet 2011
2. Need for a long-term care facility	292	RR 1.09 (0.81 to 1.46, P value 0.59)	Late tracheostomy	Terragni 2010
3. Time spent on sedation (days)	120	MD -7.09 (-14.64 to 0.45, P value 0.07, I^2 = 98%)	Early tracheostomy	Rumbak 2004 and Trouillet 2011
4. Time spent on high-dose pressors (days)	120	MD 0.50 (-1.02 to 2.02, P value 0.52)	Late tracheostomy	Rumbak 2004
5. Gastrointestinal bleed	120	RR 0.33 (0.04 to 3.11, P value 0.34)	Early tracheostomy	Rumbak 2004
6. Acute myocardial infarction	120	RR 0.50 (0.10 to 2.63, P value 0.41)	Early tracheostomy	Rumbak 2004
7. Pulmonary embolus	120	RR 1.00 (0.06 to 15.62, P value 1.00)	Early tracheostomy	Rumbak 2004

(Continued)

8. Intractable septic shock	120	RR 0.50 (0.16 to 1.57, P value 0.24)	Early tracheostomy	Rumbak 2004
9. Withdrawal of life support	120	RR 2.00 (0.19 to 21.47, P value 0.57)	Late tracheostomy	Rumbak 2004
10. Respiratory failure	120	RR 0.64 (0.26 to 1.53, P value 0.31)	Early tracheostomy	Rumbak 2004
11. Intraoperative tube dislocation	264	RR 0.55 (0.09 to 3.22, P value 0.50)	Early tracheostomy	Terragni 2010
12. Intraoperative hypoxaemia	264	RR 1.15 (0.37 to 3.53, P value 0.81)	Late tracheostomy	Terragni 2010
13. Intraoperative arrhythmia	264	No event in both groups	-	Terragni 2010
14. Endotracheal prosthesis-free days during 1 to 60 days	216	MD 1.70 (-4.52 to 7.92, P value 0.59)	Early tracheostomy	Trouillet 2011
15. Participants with reintubation or re-cannulation during 1 to 60 days	216	RR 0.48 (0.29 to 0.80, P value 0.005, NNTB = 5.9)	Early tracheostomy	Trouillet 2011
16. Sedation-free days during 1 to 28 days	216	MD 3.50 (1.05 to 5.95, P value 0.005)	Early tracheostomy	Trouillet 2011
17. Duration of intravenous sedation	120	MD -10.90 (-11.64 to -10.16, P value < 0.00001)	Early tracheostomy	Rumbak 2004
18. Duration of intravenous sedation	216	MD -3.20 (-4.97 to -1.43, P value 0.0004)	Early tracheostomy	Trouillet 2011
19. Sedation-free days at day 28	335	MD 3.76 (2.97 to 4.55, P value < 0.00001, I^2 = 0%)	Early tracheostomy	Trouillet 2011 and Zheng 2012
20. Cumulative propofol dose during 1 to 15 days, mg/kg	216	MD -34.90 (-59.73 to -10.07, P value 0.006)	Early tracheostomy	Trouillet 2011
21. Cumulative midazolam dose during 1 to 15 days, mg/kg	216	MD -3.70 (-6.55 to -0.85, P value 0.01)	Early tracheostomy	Trouillet 2011
22. Cumulative sufentanil dose during 1 to 15 days, µg/kg	216	MD -6.20 (-9.86 to -2.54, P value 0.0009)	Early tracheostomy	Trouillet 2011
23. Days (during 1 to 15 days) of haloperidol therapy	216	MD -1.30 (-2.27 to -0.33, P value 0.009)	Early tracheostomy	Trouillet 2011
24. Cumulative haloperidol dose during 1 to 15 days, mg/kg	216	MD -0.31 (-0.51 to -0.11, P value 0.002)	Early tracheostomy	Trouillet 2011
25. Bloodstream infection	276	RR 1.13 (0.75 to 1.70, P value 0.55, I^2 = 0%)	Late tracheostomy	Bösel 2013; and Trouillet 2011

(Continued)

26. Days (during 1 to 15 days) nurse-assessed as comfortable	216	MD 1.40 (0.30 to 2.50, P value 0.01)	Early tracheostomy	Trouillet 2011
27. Days (during 1 to 15 days) nurse-assessed as easy management	216	MD 1.20 (0.10 to 2.30, P value 0.03)	Early tracheostomy	Trouillet 2011
28. Received oral nutrition at 15 days	216	RR 1.57 (1.29 to 1.91, P value < 0.00001, NNTB = 3.3)	Early tracheostomy	Trouillet 2011
29. Bed-to-chair transfer at 15 days	216	RR 1.50 (1.17 to 1.94, P value 0.002, NNTB = 4.54)	Early tracheostomy	Trouillet 2011
30. Pneumothorax	264	RR 2.47 (0.10 to 59.98, P value 0.58)	Late tracheostomy	Terragni 2010
31. Subcutaneous emphysema	264	RR 2.47 (0.10 to 59.98, P value 0.58)	Late tracheostomy	Terragni 2010
32. Cannula displacement or need for replacement	264	RR 4.11 (0.20 to 84.78, P value 0.36)	Late tracheostomy	Terragni 2010
33. TT-related complications	74	RR 0.07 (0.01 to 0.51, P value 0.008, NNTB = 2.3)	Early tracheostomy	Dunham 1984
34. Major complications	74	RR 1.41 (0.47 to 4.22, P value 0.54)	Late tracheostomy	Dunham 1984
35. Self-extubation	120	RR 0.15 (0.05 to 0.46, P value 0.0009, I^2 = 0%, NNTB = 8.33)	Early tracheostomy	Rumbak 2004 and Trouillet 2011
36. Successful weaning	538	RR 1.17 (1.04 to 1.32, P value 0.009, I^2 = 6%, NNTB = 9)	Early tracheostomy	Terragni 2010 and Zheng 2012

Appendix 11. Other potentially relevant outcomes expressed as medians that were not planned in the protocol of this systematic review

Other potentially relevant and non-parametric outcomes not possible to be combined in a meta-analysis				
1. Outcome: hospital length of stay (days)				
Terragni 2010	Early tracheostomy[a]	31	17 to 39	Not available
	Late tracheostomy	32	18 to 59	
2. Outcome: Richmond Agitation Sedation Scale 5 (deeply sedated). Data presented as % of ICU stay				
Bösel 2013	Early tracheostomy	19	0 to 35	0.33
	Late tracheostomy[a]	18	3 to 63	
3. Outcome: antibiotics (% of ICU stay)				

(Continued)

Bösel 2013	Early tracheostomy[a]	67	54 to 77	0.25
	Late tracheostomy	75	59 to 88	
4. Outcome: opioids (% of ICU stay)				
Bösel 2013	Early tracheostomy[a]	64	44 to 78	0.08
	Late tracheostomy	75	58 to 86	
5. Outcome: total costs of treatment (€)				
Bösel 2013	Early tracheostomy[a]	29,033	10,291 to 68,124	0.24
	Late tracheostomy	30,546	17,352 to 12,1075	
6. Outcome: daily costs of treatment (€)				
Bösel 2013	Early tracheostomy[a]	1,760	1,707 to 1,845	0.77
	Late tracheostomy	1,745	1,660 to 1,860	
7. Outcome: antibiotic use to 30 days among survivors (antibiotic median free-days at 30 days of follow-up)				
Young 2013	Early tracheostomy	5	1 to 8	0.95
	Late tracheostomy	5	1 to 10	
8. Outcome: antibiotic use to 30 days among non-survivors (antibiotic median free days at 30 days of follow-up)				
Young 2013	Early tracheostomy[a]	2	0 to 4	0.14
	Late tracheostomy	1	0 to 5	
9. Outcome: median number of days on sedation among survivors at 30 days of follow-up				
Young 2013	Early tracheostomy[a]	5	3 to 9	< 0.001
	Late tracheostomy	8	4 to 12	
10. Outcome: median number of days on sedation among non-survivors at 30 days of follow-up				
Young 2013	Early tracheostomy[a]	5	3 to 9	0.11
	Late tracheostomy	6	4 to 10	
11. Outcome: sedatives (median % of ICU stay)				
Bösel 2013	Early tracheostomy[a]	62	28 to 55	0.02
	Late tracheostomy	62	45 to 75	

[a]Indicates the favoured group.

WHAT'S NEW

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

HISTORY

Protocol first published: Issue 3, 2008
Review first published: Issue 3, 2012

Date	Event	Description
22 December 2014	New search has been performed	In the previous version (Gomes Silva 2012), databases were searched until December 2010. We reran the searches until August 2013. We reran the searches again in October 2014. We will deal with any studies of interest when we update the review Plain language summary was adjusted according to the *Standards for the Reporting of Plain Language Summaries in New Cochrane Intervention Reviews 2013* The citation name of the lead author changed from Gomes Silva BN to Andriolo BNG
22 December 2014	New citation required and conclusions have changed	We included 4 new studies, and the quality of evidence for mortality was changed from low to moderate
19 May 2010	Amended	Contact details updated

CONTRIBUTIONS OF AUTHORS

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Conceiving of the review: BNGA and ANA.
Co-ordinating the review: BNGA and HS.
Undertaking manual searches: BNGA.
Screening search results: BNGA.
Organizing retrieval of papers: BNGA.
Screening retrieved papers against inclusion criteria: BNGA, RA and HS.
Appraising quality of papers: BNGA, RA and HS.
Abstracting data from papers: BNGA, RA and OV.
Writing to authors of papers for additional information: BNGA and RA.
Providing additional data about papers: BNGA and RA.
Obtaining and screening data on unpublished studies: BNGA and RA.
Managing data for the review: BNGA and RA.
Entering data into Review Manager (RevMan 5.1): BNGA and RA.
Analysing RevMan statistical data: HS, BNG and RA.
Performing other statistical analysis not using RevMan: RA
Performing double entry of data (data entered by person one: RA).
Interpreting data: BNGA, OV and RA.
Making statistical inferences: BNGA, HS and RA.
Writing the review: BNGA, OV and RA.
Serving as guarantor for the review (one review author): BNGA
Taking responsibility for reading and checking review before submission: OV and ANA.

DECLARATIONS OF INTEREST

Brenda NG Andriolo has been working as a respiratory therapist since 2002.

Régis B Andriolo: none known.

Humberto Saconato: none known.

Álvaro N Atallah: none known.

Orsine Valente: none known.

SOURCES OF SUPPORT

Internal sources

- No internal source of support, Brazil.

  The study was carried with the main author's own resources

External sources

- No external sources of support, Brazil.

  The study was carried with the main author's own resources

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of outcome measures

The following sentence was inserted into the final version: 'Types of outcome measures.'

Evaluation of the internal validity of included studies

At the time the protocol was prepared, the items of internal validity were compatible with those of previous versions of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c), as listed below. However, the first full version of this review was prepared according to the updated *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Additionally, all primary outcomes of this review were considered objective, specifically mortality; then the studies were considered to have low risk of bias in the item relative to 'Blinding of Participants and Personnel,' as suggested in Chapter 8: Assessing risk of bias in included studies, from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Selection bias

Was allocation concealment adequate and were data similar at baseline?

A: Adequate allocation concealment and similar descriptive data between arms at baseline.

B: Not described.

C: Not adequate.

Detection bias

Was assessment of outcomes blinded?

Met: Assessors unaware of the assigned treatment when collecting outcome measures.

Unclear: Blinding of assessor not reported and cannot be verified by contacting investigators.

Not met: Assessors aware of the assigned treatment when collecting outcome measures.

Attrition bias

Were any withdrawals described and were they acceptable?

Met: No substantial loss of participants after randomization or differences between comparison groups not statistically significant.

Unclear: Losses not reported by study authors.

Not met: Substantial loss of participants after randomization or statistically significant difference in losses between comparison groups.

Performance bias

We will not use blinding of providers and participants as a criterion to assess internal validity of included trials because of the nature of the intervention.

Sensitivity analysis

Inclusion of a study with different times of early and late tracheostomies than were put forth in our inclusion criteria was considered in a sensitivity analysis.

Description of included studies

In the first version of this systematic review (Gomes Silva 2012), we considered that the numbers of participants from randomization to analysis of each outcome were not clearly reported for each of the comparison groups in Terragni 2010. Therefore this study was considered to have high risk of bias. However, intention-to-treat analysis (ITT) was properly performed by the review authors. Withdrawals at one year of follow-up were as follows: n = 10 (4.78%) in the early tracheostomy group and n = 4 (1.9%) in the late tracheostomy group.

INDEX TERMS

Medical Subject Headings (MeSH)

Critical Care [*methods]; Critical Illness [mortality] [*therapy]; Length of Stay [statistics & numerical data]; Pneumonia [mortality]; Randomized Controlled Trials as Topic; Respiration, Artificial [statistics & numerical data]; Time Factors; Tracheostomy [adverse effects] [*methods] [mortality]

MeSH check words

Humans