

Protocolized Versus Nonprotocolized Weaning to Reduce the Duration of Invasive Mechanical Weaning in Neonates

A Systematic Review of All Types of Studies

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ABSTRACT

Mechanical ventilation is one of the most commonly used treatments in neonatology. Prolonged mechanical ventilation is associated with deleterious outcomes. To reduce the ventilation duration, weaning protocols have been developed to achieve extubation in adult and pediatric care in a safe and uniform manner. We performed a systematic review to obtain all available evidence on the effect of pro-

colized versus nonprotocolized weaning on the duration of invasive mechanical ventilation in critically ill neonates. The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, Web of Science, and the International Clinical Trial Registry Platform were searched until January 2018. Quantitative and qualitative studies involving neonates that investigated or described protocolized versus nonprotocolized weaning were included. Primary outcome was the difference in weaning duration. A total of 2099 potentially relevant articles were retrieved. Three studies met the inclusion criteria. Of 2 of these, the separate neonatal data could not be obtained. Only one retrospective study was included for this review. This reported a decrease in the mean weaning time from 18 to 5 and 6 days, respectively. There is no robust evidence in the literature to support or disprove the use of a weaning protocol in critically ill neonates.

Key Words: infant, intensive care units, neonatal, neonatology, newborn, ventilator weaning

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Mechanical ventilation (MV) is one of the most commonly used treatments in neonatology. Both invasive and noninvasive techniques are extensively used for respiratory support in term and preterm born neonates.¹ In recent years, there has been growing awareness that invasive ventilation has deleterious effects such as bronchopulmonary dysplasia and developmental problems and should be applied/administered as short as possible.^{2,3} To prevent these effects, neonates are weaned off the ventilator and extubated as soon as possible, although 30% to 40% will require a reintubation.³ Extubation

failure is associated with an increased risk of morbidity and mortality⁴; therefore, it is important to attempt extubation at the time when successful extubation is likely. Weaning protocols are still little used but could be useful to achieve extubation in a safe, uniform, and less variable way. Decisions on weaning from MV seem to be influenced by many factors such as nursing involvement, adherence to a protocol, or patient to healthcare provider ratio.⁴⁻⁶ There is strong evidence for the benefit of a weaning protocol in adults, and up to 70% adult intensive care units (ICUs) have implemented weaning protocols.⁷ In both the adult and pediatric ICUs, the evidence favors protocolized weaning over nonprotocolized weaning, although the evidence in the pediatric intensive care unit (PICU) is less compelling.^{8,9}

Weaning protocols are also used in neonatal intensive care (NICU), although less intensively. A study on periextubation practices in extremely preterm infants showed that only 36% of the responding units used a guideline or written protocol.⁴ A Canadian survey confirmed this; 38% of the tertiary NICUs had a protocol to guide the use of MV.¹⁰ The evidence for using these protocols in the NICU is scarce. Wielenga et al¹¹ in 2016 published a Cochrane review on protocolized versus nonprotocolized weaning for invasively ventilated neonates. Randomized controlled trials (RCTs) on this subject were not found, and conclusions could not be drawn.

Therefore, the aim of this study was to evaluate and conduct a systematic review of all available evidence for protocolized weaning versus nonprotocolized weaning during invasive MV in neonates.

METHODS

The method and search strategy were registered in Prospero (ID CRD42016032412).

Population and setting

Both quantitative and qualitative studies investigating protocolized weaning compared with nonprotocolized weaning practices and that involved neonates were included. Neonates were defined as a child younger than 28 completed days after the expected date of birth (World Health Organization [WHO] definition).¹²

The corresponding authors of studies including both neonates and infants were asked to provide separate data for analysis in this review. If data separation was not possible, these studies were included only if the neonatal sample made up more than 75% of the population sample. Studies were included in which neonates exclusively were mechanically ventilated by an endotracheal tube; therefore, studies in which infants received ventilation by noninvasive techniques or tracheostomy were excluded. Extubation readiness assessment as a

single intervention (eg, Spontaneous Breathing Trial) was not considered as a weaning protocol.

Intervention and comparator

For this review, protocolized weaning was defined as having used any kind of protocol, with the intention to discontinue invasive MV. Nonprotocolized weaning was defined as usual care, for example, standard practice that incorporated any nonprotocolized practice.

All sorts of interventions and comparators were included; for example, a protocol versus standard care. All kinds of professionals were involved, a comparison between a protocol led by the nursing team versus standard care by the registrars or a computerized protocol versus standard care.

Outcomes

In accordance with the ventilation core outcome set developed by Ringrow and colleagues,¹³ we extracted data on mortality, health-related quality of life (HRQOL), duration of MV, reintubation, length of stay (LOS), and successful extubation.

Types of study

Both quantitative and qualitative studies were included. The quantitative studies could be (semi)-RCTs, nonrandomized, or cohort studies. Qualitative studies could be case reports or interviews.

Search strategy

This systematic review followed the guidelines outlined in the Preferred Reporting Items for Systematic literature reviews and Meta-Analysis (PRISMA) statement.¹⁴ The study protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (No. CRD42016032412). The review team, with the help of a biomedical information specialist from the medical library of the Erasmus University Medical Center, devised and executed the search strategy. The following databases were searched: the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, Web of Science, and the International Clinical Trial Registry Platform. The specific search strategy for each database is presented (see Table 1). Key words such as “protocol,” “weaning,” “mechanical ventilation,” “extubation,” and “neonates” were used in the search strategy. Furthermore, the reference lists of the identified articles were hand-searched for additional references. Ongoing studies were identified by searching the major clinical trial registries. There was no language restriction.

All databases were searched until January 2018.

Table 1. Literature search, until January 18, 2018

	<i>n</i>	Doubles excluded
EMBASE ^a	1072	1052
MEDLINE Ovid ^b	596	116
Web of Science ^c	436	115
Cochrane Central ^d	136	5
Scopus ^e	1137	443
CINAHL ^f	234	51
Google Scholar ^g	200	171
ProQuest Dissertations and Theses ^h	59	58
ClinicalTrials.gov ⁱ	88	88
Total	3958	2099

^a**EMBASE:** ((extubation/de OR (extubat* OR detubat*):ab,ti) OR (('artificial ventilation'/exp OR ventilator/de OR 'assisted ventilation'/exp OR ((respirat* OR breathing OR airway*) NEAR/3 (movement* OR artificial* OR assisted OR pressure* OR support* OR mechanic*)) OR ventilat* OR Respiator OR Respirators):ab,ti) AND (wean* OR liberat* OR withdraw*):ab,ti) AND ('computer assisted therapy'/exp OR 'pressure support ventilation'/de OR 'high frequency ventilation'/de OR 'pressure control mechanical ventilation'/de OR 'volume control mechanical ventilation'/de OR ((computer OR proportion*) NEAR/3 assist*) OR (automat* NEAR/3 system*) OR (smart NEAR/3 care) OR smartcare OR automode OR (adaptive NEAR/3 (support* OR assist*)) OR (mandatory NEAR/3 minute*) OR (neurally NEAR/3 adjust*) OR nava OR (volume NEAR/3 support) OR (pressure NEAR/3 support) OR psv OR (high NEAR/3 frequenc*) OR hfov):ab,ti OR ('practice guideline'/de OR (protocol* OR guideline*):ab,ti) AND (newborn/exp OR infant/exp OR 'newborn disease'/exp OR 'newborn intensive care'/de OR (newborn* OR (new* NEXT/1 born*) OR neonat* OR infant* OR baby OR babies OR (month* NEAR/3 age*) OR prematur* OR dysmatur*):ab,ti)

^b**MEDLINE OvidSP:** (('Airway Extubation'/OR (extubat* OR detubat*):ab,ti) OR 'ventilator weaning'/OR ((exp "Respiration, Artificial"/OR "Ventilators, Mechanical"/OR ((respirat* OR breathing OR airway*) ADJ3 (movement* OR artificial* OR assisted OR pressure* OR support* OR mechanic*)) OR ventilat* OR Respiator OR Respirators):ab,ti) AND (wean* OR liberat* OR withdraw*):ab,ti) AND ("Therapy, Computer-Assisted"/OR "High-Frequency Ventilation"/OR ((computer OR proportion*) ADJ3 assist*) OR (automat* ADJ3 system*) OR (smart ADJ3 care) OR smartcare OR automode OR (adaptive ADJ3 (support* OR assist*)) OR (mandatory ADJ3 minute*) OR (neurally ADJ3 adjust*) OR nava OR (volume ADJ3 support) OR (pressure ADJ3 support) OR psv OR (high ADJ3 frequenc*) OR hfov):ab,ti. OR ("Practice Guidelines as Topic"/OR "Guidelines as Topic"/OR (protocol* OR guideline*):ab,ti) AND (exp infant/OR "Intensive Care, Neonatal"/OR (newborn* OR (new* ADJ3 born*) OR neonat* OR infant* OR baby OR babies OR (month* ADJ3 age*) OR prematur* OR dysmatur*):ab,ti)

^c**Web of Science:** TS=(((extubat* OR detubat*))) OR (((respirat* OR breathing OR airway*) NEAR/3 (movement* OR artificial* OR assisted OR pressure* OR support* OR mechanic*)) OR ventilat* OR Respiator OR Respirators) AND (wean* OR liberat* OR withdraw*) AND (((computer OR proportion*) NEAR/3 assist*) OR (automat* NEAR/3 system*) OR (smart NEAR/3 care) OR smartcare OR automode OR (adaptive NEAR/3 (support* OR assist*)) OR (mandatory NEAR/3 minute*) OR (neurally NEAR/3 adjust*) OR nava OR (volume NEAR/3 support) OR (pressure NEAR/3 support) OR psv OR (high NEAR/3 frequenc*) OR hfov) OR ((protocol* OR guideline*))) AND ((newborn* OR (new* NEAR/1 born*) OR neonat* OR infant* OR baby OR babies OR (month* NEAR/3 age*) OR prematur* OR dysmatur*))

^d**Cochrane Central:** ((extubat* OR detubat*):ab,ti) OR (((respirat* OR breathing OR airway*) NEAR/3 (movement* OR artificial* OR assisted OR pressure* OR support* OR mechanic*)) OR ventilat* OR Respiator OR Respirators):ab,ti) AND (wean* OR liberat* OR withdraw*):ab,ti) AND (((computer OR proportion*) NEAR/3 assist*) OR (automat* NEAR/3 system*) OR (smart NEAR/3 care) OR smartcare OR automode OR (adaptive NEAR/3 (support* OR assist*)) OR (mandatory NEAR/3 minute*) OR (neurally NEAR/3 adjust*) OR nava OR (volume NEAR/3 support) OR (pressure NEAR/3 support) OR psv OR (high NEAR/3 frequenc*) OR hfov):ab,ti OR ((protocol* OR guideline*):ab,ti) AND ((newborn* OR (new* NEAR/1 born*) OR neonat* OR infant* OR baby OR babies OR (month* NEAR/3 age*) OR prematur* OR dysmatur*):ab,ti)

^e**Scopus:** TITLE-ABS-KEY (((extubat* OR detubat*))) OR (((respirat* OR breathing OR airway*) W/3 (movement* OR artificial* OR assisted OR pressure* OR support* OR mechanic*)) OR ventilat* OR Respiator OR Respirators) AND (wean* OR liberat* OR withdraw*) AND (((computer OR proportion*) W/3 assist*) OR (automat* W/3 system*) OR (smart W/3 care) OR smartcare OR automode OR (adaptive W/3 (support* OR assist*)) OR (mandatory W/3 minute*) OR (neurally W/3 adjust*) OR nava OR (volume W/3 support) OR (pressure W/3 support) OR psv OR (high W/3 frequenc*) OR hfov) OR ((protocol* OR guideline*))) AND ((newborn* OR (new* W/1 born*) OR neonat* OR infant* OR baby OR babies OR (month* W/3 age*) OR prematur* OR dysmatur*))

^f**CINAHL:** ((MH "Extubation+" OR (extubat* OR detubat*)) OR MH "ventilator weaning+" OR ((MH "Respiration, Artificial+" OR MH "Ventilators, Mechanical+" OR ((respirat* OR breathing OR airway*) N3 (movement* OR artificial* OR assisted OR pressure* OR support* OR mechanic*)) OR ventilat* OR Respiator OR Respirators) AND (wean* OR liberat* OR withdraw*)) AND (MH "Therapy, Computer-Assisted+" OR MH "Ventilation, High Frequency+" OR ((computer OR proportion*) N3 assist*) OR (automat* N3 system*) OR (smart N3 care) OR smartcare OR automode OR (adaptive N3 (support* OR assist*)) OR (mandatory N3 minute*) OR (neurally N3 Nust*) OR nava OR (volume N3 support) OR (pressure N3 support) OR psv OR (high N3 frequenc*) OR hfov) OR (MH "Practice Guidelines+" OR (protocol* OR guideline*))) AND (MH infant+ OR MH "Intensive Care, Neonatal+" OR (newborn* OR (new* N born*) OR neonat* OR infant* OR baby OR babies OR (month* N3 age*) OR prematur* OR dysmatur*))

^g**Google Scholar:** Ventilation|ventilator|artificial|mechanical|supported respiration|breathing|respirator|respirators weaning|withdrawal|liberation "computer assisted"|automated|adaptive support|assistance|mandatory-minute newborns|infants|premature|neonates

^hProQuest Dissertations and Theses

(ti(Ventilat* OR "artificial respiration " OR "mechanical respiration " OR "supported respiration " OR respirator*) OR ab(Ventilat* OR "artificial respiration " OR "mechanical respiration " OR "supported respiration " OR respirator*)) AND (ti(wean* OR withdraw* OR liberation) AND ab(newborn* OR infant* OR prematur* OR neonat*)) OR ab(wean* OR withdraw* OR liberation) AND ab(newborn* OR infant* OR prematur* OR neonat*))

ⁱ**ClinicalTrials.gov:** (Ventilat* OR "artificial respiration " OR "mechanical respiration " OR "supported respiration " OR respirator*) AND (wean* OR withdraw* OR liberation) AND (newborn* OR infant* OR prematur* OR neonat*)

<http://www.controlled-trials.com/>; <http://portal.nihr.ac.uk/Pages/default.aspx>; <http://public.ukcrn.org.uk/search/>; and www.clinicaltrials.gov.

A search for theses was performed in: www.theses.com; and <https://etd.ohiolink.edu>.

A search for conference proceedings was performed in:

- ISI Conference Proceedings (1990 to present)
- Annual Meetings of the Pediatric Academic Societies (to present),
- The European Paediatric Society (1990 to present), and
- The Perinatal Society of Australian & New Zealand (1993 to present).

Study selection

The review team consisted of 6 researchers (B.B., J.W., A.vd.H., H.v.Z., P.M., O.H.), divided into 3 pairs. These pairs independently scanned the titles and abstracts of citations identified by the electronic search. Records not meeting the eligibility requirements were excluded.

Full-text copies of all potentially relevant studies were obtained. In case of disagreements, consensus was strived for thorough discussion or consultation of a third researcher. Details of the excluded studies are noted in Table 2.

Table 2. Included articles after first screening

Study: Author (year)	Reason for inclusion or exclusion	Inclusion/Exclusion
Barker and Spence (2014) ¹⁵	Abstract presented at the Perinatal Society of Australia & New Zealand 2014. No full-text article available. Single-center, prospective, nonblinded cohort study; NICU setting. 111 episodes, between January and October 2013; 30% of the population was weaned using a protocol. This resulted in a reduction of duration of 2.4 vs 3.5 d. <i>Request for the unpublished data from the authors.</i>	Included
Barker et al (2015) ¹⁶	Abstract presented at the Perinatal Society of Australia & New Zealand 2015. No full-text article available. Single-center, retrospective cohort study, measuring the compliance with a weaning protocol and the effect on duration of ventilation; NICU setting. Continuation of the article in 2014. Compliance improved, resulting in a reduction of duration of MV of 1.9 vs 2.4 d ($P > .5$). <i>Request for the unpublished data from the authors.</i>	Included
Carlo et al (1986) ¹⁷	Single-center cohort study; NICU population. A computer algorithm vs standard interpretation of arterial blood gas values. The effect on the correction of blood gas derangements was compared.	Excluded
Demaray and Sittig (2007) ¹⁸	Review of weaning protocols in the pediatric and adult ICUs. The article could not be retrieved/found at the journal's Web site.	Excluded
Hermeto et al (2009) ¹⁹	Retrospective study, a new weaning protocol for the neonatal population. Development of clinical weaning guidelines for respiratory therapists. A pretest, posttest, second posttest surveys were measured; 93, 109, and 99 neonates were included. Time to first extubation was shortened (median 5, 1.5, and 1.2 d, respectively) and duration of MV (18, 5, and 6 d, respectively).	Included
Jouvet et al (2013) ²⁰	Abstract of oral presentation at the European Society of Paediatric and Neonatal Intensive Care 2013, on the evidence of using weaning protocols in the pediatric and adult ICUs.	Excluded
Keogh et al (2003) ²¹	Single-center intervention study; PICU population; no neonates included. Historic cohort vs prospective cohort after implementing weaning guidelines. Both total ventilation time and LOS were longer postintervention (median difference: total ventilation time = -15.8 h, $P < .068$; and LOS = -23.75 h, $P < .088$).	Excluded
Luyt et al (2002) ²²	Single-center, prospective, randomized controlled trial; NICU population; 50 neonates were included. Nurse- vs registrar-led weaning, with a weaning protocol. Both groups used the same protocol. Twenty-five neonates were nurse-led weaned (weaning time: 1200 min; 95% CI, 621-1779) vs 23 neonates registrar-led weaned (weaning time: 3015 min; 95% CI, 2650-3380); $P = .0458$.	Excluded
Randolph et al (2002) ²³	No comparison of protocolized vs nonprotocolized weaning was described. Multicenter, randomized controlled trial 182 children admitted to the PICU requiring ventilator support for more than 24 h randomly assigned; 3 excluded, 179 evaluated among whom 31 were neonates.	Included
Restrepo et al (2004) ²⁴	<i>Request for the unpublished data from the authors.</i> Single-center, prospective cohort study; use of a ventilator management protocol vs standard nonprotocol-based care on the duration of weaning time. Overall ventilator duration was not significantly different. Ventilator management protocol patients had a shorter weaning time (17.5 h; range, 1-181 h) than nonprotocol patients (35 h; range, 0.5-377 h; $P = .005$). PICU population; no neonates were included according to the authors. Patient age—pretest: median = 48 mo (range, 0.5-216 mo); posttest: median = 19 mo (range, 0.5-252 mo)	Excluded

(continues)

Table 2. Included articles after first screening (*Continued*)

Study: Author (year)	Reason for inclusion or exclusion	Inclusion/Exclusion
Rushfort (2005) ²⁵	A single-center, randomized controlled trial to compare outcomes between medical-led and nurse-led (protocol-directed) weaning from MV in a PICU setting. Patient age was 2-7 wk. No comparison between protocolized versus nonprotocolized weaning was described.	Excluded
Schultz et al (2001) ²⁶	The study could draw no conclusions because of recruitment problems. Single-center, multiunit, randomized controlled trial 223 children requiring intubation and MV; 4 did not reach study end point; 219 evaluated; sample includes neonates <i>Request for the unpublished data from the authors.</i>	Included
Sinha and Donn (2006) ²⁷	Describing 2 case studies of the weaning process in neonates. No protocol was used.	Excluded
West and Pope (2010) ²⁸	Retrospective audit in a single center; NICU population. Extubation failure described in relation to the adherence of the nursing guidelines during this period.	Excluded

Abbreviations: ICU, intensive care unit; MV, mechanical ventilation; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit.

Data extraction

Of the eligible articles, the study design, setting, patient characteristics, (co-)interventions, outcome measurements, conclusions, comments, and quality assessments were documented. A data extraction form was used to collect author, year, design, sample, time points, length of measurement, target range, and key results. The extracted data were sent to the corresponding author of the study concerned to verify whether the data were abstracted correctly. If necessary, the corresponding author was asked to provide missing data.

Quality assessment and grading

We graded the quality of the selected studies using the QualSyst tool for quantitative and qualitative studies by Kmet et al.²⁹ The QualSyst tool for quantitative studies is a validated generic checklist consisting of 14 items with scores from 0 to 2 and the possibility to score "not applicable" (see Table 3). Study quality was not considered an exclusion criterion. An assessment tool adapted from Gartner et al³⁰ was used to determine the strength of the evidence. The levels of evidence were defined as follows: (1) strong evidence, that is, statistically significant results among 50% of the tested relationships in longitudinal studies; (2) moderate evidence, that is, statistically significant results in cross-sectional studies; (3) limited evidence, that is, statistically significant results in one study; (4) expert evidence, that is, an indication from 1 or more narrative reviews; (5) inconclusive evidence, that is, statistically significant results in a cross-sectional study and 50% of the relationships or less were statistically significant; and (6) inconsistent evidence, that is, statistically significant results were found, but they were in different directions.

Data extraction and synthesis

As only a few articles were expected to be included, a meta-analysis of the results would not seem feasible. The characteristics of the studies are presented as descriptive statistics. The study outcome results are presented in a tabular form.

RESULTS

The initial search yielded 2099 potentially relevant articles. After screening of the titles and abstracts (see Figure 1), 14 articles that met the inclusion criteria remained for further evaluation (see Table 2). After full-text reading, we excluded 7 articles: Carlo et al,¹⁷ Demaray and Sittig,¹⁸ Jouvet et al,²⁰ Keogh et al,²¹ Luyt et al,²² Sinha and Donn,²⁷ and West and Pope.²⁸ Barker and colleagues^{15,16} published data of 2 studies as congress abstracts. Until now, however, these studies have not been published in peer-reviewed journals. Barker and colleagues were contacted but could not provide the unpublished data. These abstracts were not included.

Five articles met the criteria for inclusion in this review: Hermeto et al,¹⁹ Randolph et al,²³ Restrepo et al,²⁴ Rushfort,²⁵ and Schultz et al.²⁶ Four studies conducted at a PICU also included neonates: Randolph et al,²³ Restrepo et al,²⁴ Rushfort,²⁵ and Schultz et al.²⁶ The authors were invited by e-mail to provide the specific neonatal data. Rushfort²⁵ and Restrepo et al²⁴ replied that neonates (in accordance to the WHO definition) were not included in their studies. Randolph et al²³ and Schultz et al²⁶ could not provide the separate neonatal data. As the neonatal sample in their studies made up less than 75% of the total sample, their studies were excluded as well.

Table 3. Checklist for assessing the quality of quantitative studies^{a,b,c}

	Criteria	Yes (2)	Partial (1)	No (0)	N/A
1	Question/objective sufficiently described?	x x			
2	Study design evident and appropriate?	x x			
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?	x	x		
4	Subject (and comparison group, if applicable) characteristics sufficiently described?	x x			
5	If interventional and random allocation was possible, was it described?				x x
6	If interventional and blinding of investigators was possible, was it reported?				x x
7	If interventional and blinding of subjects was possible, was it reported?				x x
8	Outcome and (if applicable) exposure measure(s) well-defined and robust to measurement/misclassification bias? Means of assessment reported?		x x		
9	Sample size appropriate?	x	x		
10	Analytic methods described/justified and appropriate?	x x			
11	Some estimate of variance is reported for the main results?	x x			
12	Controlled for confounding?				x x
13	Results reported in sufficient detail?	x x			
14	Conclusions supported by the results?	x x			

^aRating article Hermeto et al¹⁹; P. Mansvelt and J. M. Wielenga.

^bTotal sum = (number of "yes" * 2) + (number of "partials" * 1).

Total possible sum = 28 - (number of "N/A" * 2).

Summary score: total sum/total possible sum.

Total sum = (16) + (2). Total possible sum = 28 - (8).

Summary score: 18/20 = 0.90.

Total sum = (16) + (2). Total possible sum = 28 - (8).

Summary score: 18/20 = 0.90.

^cFrom Kmet et al.²⁹

Thus, one study met the inclusion criteria: Hermeto et al.¹⁹ This study was a retrospective study conducted in a single-center tertiary NICU in Canada. Three periods were distinguished: 1 year before a comprehensive ventilation protocol had been implemented (control group) and 1 and 2 years after this protocol had been implemented. In 3 years, more than 300 neonates were studied ($n = 93/99/109$, respectively). Their gestational age was 27 ± 2 weeks (mean \pm SD) in all 3 periods. The median duration of MV had decreased from 18 days in the period prior to the intervention to 5 days after 1 year and 6 days after 2 years. The differences in median duration of MV between the period prior to the implementation of the protocol and the periods after 1 and 2 years were significant ($P < .05$). Neither the mortality rate nor the occurrences of bronchopulmonary dysplasia, air leak syndrome, and pneumonia significantly differed between these study periods. The extubation failure rate was 40%, 26%, and 20%, respectively.

Data analysis per birth weight group yielded similar results. Extubation failure was significantly lower in the smallest group, 500 to 750 g.

In accordance with the core outcome set developed by Ringrow and colleagues,¹³ the items HRQOL and LOS were not reported in the study by Hermeto et al.¹⁹

Study quality graded with the QualSyst tool²⁹ resulted in an average score of 18, out of a maximum of 20 points. The quality of this study was considered good. According to the assessment with the adapted tool by Gartner et al,³⁰ the evidence of this review should be considered as limited.

DISCUSSION

There is limited evidence about the effectiveness of protocolized weaning for neonates. With regard to the primary outcome, only one study was included in this review.¹⁹ This study included a large group of neonates, its methodological quality was good, and the results were encouraging.

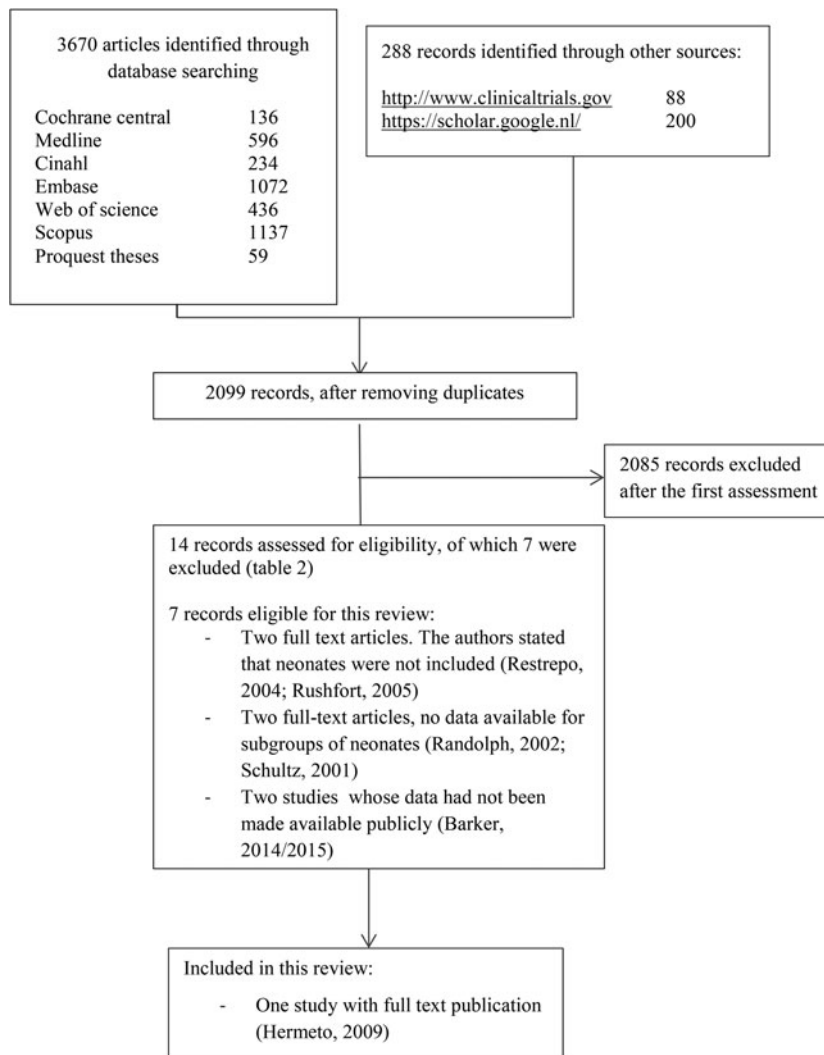


Figure 1. Study inclusion flowchart.

Barker and colleagues^{15,16} performed a comparable study in an NICU population, the data of which were published as 2 congress abstracts. The use of a weaning protocol had resulted in a reduction in the mean number of ventilation days from 3.5 to 2.4 days ($P = .55$). A follow-up of this study in 2015 reported a further reduction of 0.5 ventilation days (ns). Although the results are promising, it is difficult to interpret the validity of these studies: no power analysis was described, and these studies have not been published in a peer-reviewed journal. Therefore, these data could not contribute to this review to evaluate the effectiveness of protocolized weaning in neonates.

Despite the lack of evidence applying a protocol or guideline is one of the most frequently used practices in the weaning process, but a wide variation exists in “weaning” practices, all aimed to extubate as soon as possible.⁴ Also different MV strategies can

be applied.³¹ Currently, volume-targeted ventilation is preferred compared with pressure-limited ventilation.³² Volume-targeted ventilation aims to produce a more stable tidal volume in order to reduce lung injury. Spontaneous breathing trials are used to predict successful extubation in ventilated preterm infants.³³⁻³⁵ Also, new ventilation modalities wean patients automatically.^{36,37} Several ways to assess extubation readiness have been studied in neonates, using respiratory scores and measurements.^{38,39} These alternative weaning strategies could make the need for a weaning protocol less compelling. However, not only the ventilator weaning strategy itself but also the use of supportive medication such as caffeine or steroids, indication for extubation, and postextubation support could be part of a practical comprehensive weaning protocol.⁴⁰ Although extubation failure is reduced by applying nasal intermittent positive pressure ventilation

instead of continuous positive pressure ventilation, no effect on chronic lung disease or mortality is achieved.⁴¹ Currently, a large multicenter RCT of sedation and weaning in 18 PICUs in the United Kingdom is underway and is actively recruiting approximately 14 000 children and neonates (Blackwood et al, 2018: <http://www.isrctn.com/ISRCTN16998143>). The weaning protocol includes daily screening for readiness to wean and a spontaneous breathing trial. The outcomes of this RCT may provide further useful information pertinent to protocolized weaning in neonates.

Strengths of this review are the following: The review team was very familiar with this topic and the literature as they previously had performed a Cochrane review on this topic. The extensive literature search was performed with the help of a specialist of the medical library. The study selection was performed by several pairs separately. The quality of the articles was taken into account in the final conclusions. Validated instruments were used to assess the methodological and strength of the studies. A Prospero protocol had been submitted in advance (ID CRD42016032412).

A possible limitation is that neonatal data from the eligible studies in pediatric settings could not be made available. These could have provided extra evidence. Loosening the inclusion criteria in terms of type of studies did not provide any additional evidence. Only the large international search sites were screened; regional or national sites were not searched. Relevant studies in language other than English might therefore have been missed.

CONCLUSION

Because of a lack of studies, there is no robust evidence to support or disprove the use of a weaning protocol for the discontinuation of MV in neonates. Only one study showed encouraging results, but a new study is underway (Blackwood et al, 2018: <http://www.isrctn.com/ISRCTN16998143>). Studies particularly focused on neonates should be undertaken to provide specific guidance for neonatal clinicians.

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