**QUEEN'S
UNIVERSITY
BELFAST**

Protocolized versus non-protocolized weaning to reduce the duration of invasive mechanical weaning in neonates: a systematic review of all types of studies

Bol, B., van Zanten, H., Wielenga, J., vd Hoogen, A., Mansvelt, P., Blackwood, B., & Helder, O. (2019). Protocolized versus non-protocolized weaning to reduce the duration of invasive mechanical weaning in neonates: a systematic review of all types of studies. *Journal of Perinatal and Neonatal Nursing*. <https://doi.org/10.1097/JPN.0000000000000411>

Published in:
Journal of Perinatal and Neonatal Nursing

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

Publisher rights

© 2019 Wolters Kluwer Health, Inc. This work is made available online in accordance with the publisher's policies. Please refer to any applicable terms of use of the publisher.

General rights

Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

1 **Protocolized versus non-protocolized weaning to reduce the duration of invasive** 2 **mechanical weaning in neonates: a systematic review of all types of studies.**

3 Bas Bol, RN MANP^{1*}, Henriette van Zanten RN PhD ^{2*}, Joke Wielenga RN PhD³, Agnes vd Hoogen RN PhD⁴,
 4 Petri Mansvelt RN MANP⁵, Bronagh Blackwood RN PhD⁶, Onno Helder RN PhD¹.

5 ** Bas Bol and Henriette van Zanten contributed equally at this manuscript.*

6 Corresponding author: Bas Bol, s.bol@erasmusmc.nl. Erasmus MC - Sophia Children's Hospital, Rotterdam, The
 7 Netherlands. Wytemaweg 80, postal code 3015CM. Tel: +31107036838.

8
 9 ¹Department of Pediatrics, Division of Neonatology, Erasmus Medical Center Rotterdam – Sophia Children's
 10 Hospital, Rotterdam, The Netherlands. ²Neonatal Intensive Care Unit, Leiden University Medical Center, Leiden,
 11 The Netherlands. ³Intensive Care Neonatology, Amsterdam University Medical Centers, location Academic Medical
 12 Centre, Amsterdam, The Netherlands. ⁴Department of Neonatology, Wilhelmina Children's Hospital, University
 13 Medical Center, Utrecht, The Netherlands. ⁵Department of Neonatology, Amalia Children's Hospital, Radboud
 14 University Medical Center, Nijmegen, The Netherlands. ⁶Center for Experimental Medicine, School of Medicine,
 15 Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, United Kingdom.

16 17 **Acknowledgements:**

18 We would like to thank:
 19 Wichor Bramer (Biomedical information specialist), Medical Library,
 20 Erasmus MC, Erasmus University Rotterdam, The Netherlands
 21
 22 Ko Hagoort, inhouse-editor
 23 Erasmus MC, Erasmus University Rotterdam, The Netherlands.

24 **Funding:** No fundings were received
 25

Abstract:

Mechanical ventilation is one of the most 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 protocolized versus non-protocolized weaning on the duration of invasive mechanical ventilation in critically ill neonates.

The Cochrane Central Register of Controlled Trials; MEDLINE; EMBASE; CINAHL were searched; Web of Science; and the International Clinical Trial Registry Platform, until January 2018. Quantitative and qualitative studies involving neonates which investigated or described protocolized versus non-protocolized 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 two 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.

Conclusion: There is no robust evidence in the literature to support or disprove the use of a weaning protocol in critically ill neonates.

Keywords: Infant, newborn. Intensive care units, neonatal. Neonatology. Ventilator weaning

Abbreviations:

CI –confidence interval

HRQoL – health related quality of life

ICU – intensive care unit

LOS – length of stay

MV – mechanical ventilation

NICU – neonatal intensive care unit

NS - not significant

PICU – pediatric intensive care unit

RCT – randomized controlled trial

54 SD – standard deviation

55 VTV- volume targeted ventilation

56 WHO – world health organization

57

58 **Precis:**

59 Invasive mechanical ventilation is one of the most used treatments in neonatology. The evidence for protocolized
60 weaning off mechanical ventilation is very limited.

61

62

63

64

Introduction:

Mechanical ventilation (MV) is one of the most used treatments in neonatology. Both, invasive and non-invasive 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 30-40% will require a reintubation (3). Extubation failure is associated with increased risk of morbidity and mortality (4), 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 unit have implemented these (7). Both, in the adult and in the pediatric intensive care unit (PICU) the evidence favours protocolized weaning over non-protocolized weaning, although the evidence in the PICU is less compelling (8, 9).

Weaning protocols are also used in neonatal intensive care (NICU) , although less intensively. A study on peri-extubation 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 al. in 2016 published a Cochrane review on protocolized versus non-protocolized weaning for invasively ventilated neonates (11). Randomized controlled trials (RCT) 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 non-protocolized weaning during invasive MV in neonates.

Method:

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

Population and setting

Both, quantitative and qualitative studies investigating protocolized weaning compared to non-protocolized weaning practices, and which involved neonates, were included. Neonates were defined as a child under 28 completed days after the expected date of birth (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 endotracheal tube; therefore studies in which infants received ventilation by non-invasive techniques or tracheostomy were excluded. Extubation readiness assessment as a single intervention (e.g. 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 mechanical ventilation.

Non-protocolized weaning was defined as usual care, e.g. standard practice that incorporated any non-protocolized practice.

All sorts of interventions and comparators were included; e.g. 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 mechanical ventilation, re-intubation, length of stay (LOS), and successful extubation.

Types of study

Both quantitative and qualitative studies were included. The quantitative studies could be (semi-)randomized controlled trials, non-randomized, 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 (CRD, No. 42016032412). The review team, including a librarian 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 (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 trials registries. There was no language restriction.

All databases were searched from start of the digital databank until January 2018.

Study selection

The review team consisted of six researchers (BB, JW, AvdH, HvZ, PM, OH), divided into three 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 through discussion or consultation of a third researcher. Details of the excluded studies are noted in table 2.

Data extraction

Of 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 if 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 (15). The QualSyst tool for quantitative studies is a validated generic checklist consisting of 14 items with scores from zero to two and the possibility to score 'not applicable'. Study quality was not considered an exclusion

criterion. An assessment tool adapted from Gartner (16) was used to determine the strength of the evidence. The levels of evidence were defined as: (1) strong evidence, i.e., statistically significant results among 50% of the tested relationships in longitudinal studies; (2) moderate evidence, i.e., statistically significant results in cross-sectional studies; (3) limited evidence, i.e., statistically significant results in one study; (4) expert evidence, i.e., an indication from one or more narrative reviews; (5) inconclusive evidence, i.e., statistically significant results in a cross-sectional study and 50% of the relationships or less were statistically significant; and (6) inconsistent evidence, i.e., 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 tabular form.

Results:

The initial search yielded 2099 potentially relevant articles. After screening of the titles and abstracts (figure 1) 14 articles that met the inclusion criteria remained for further evaluation (table 2). After full text reading we excluded seven articles: Carlo (17), Demaray (18), Jouvet (19), Keogh (20), Luyt (21), Sinha (22), and West (23). Barker published data of two studies as congress abstracts (24, 25). Until now, however, these studies have not been published in peer reviewed journals. Barker was contacted, but could not provide the unpublished data. The abstracts were not included.

Five articles met the criteria for inclusion in this review; Hermeto (26), Randolph (27), Restrepo (28), Rushfort (29) and Schultz (30). Four studies conducted on a pediatric intensive care unit also included neonates ((Randolph (27), Restrepo (28), Rushfort (29), and Schultz (30)). The authors were invited by e-mail to provide the specific neonatal data. Rushfort (29) and Restrepo (28) replied that neonates (in accordance to the WHO definition) were not included in their studies. Randolph (27) and Schultz (30) could not provide the separate neonatal data. As, moreover, the neonatal sample in their studies made up less than 75% of the total sample, their studies were excluded as well.

Thus, one study met the inclusion criteria: Hermeto (26). This study was a retrospective study performed in a single center tertiary NICU in Canada. Three periods were distinguished: one year before a comprehensive ventilation protocol had been implemented (control group) and 1 and 2 years after this had been implemented. In three years, over 300 neonates were studied (n = 93/99/109 respectively). Their mean gestational age was 27 ± 2 weeks (mean $\pm$ SD) in all three periods. The median duration of MV had decreased from 18 days in the period prior to the intervention, to 5 days after one 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 ($p < 0.05$).

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 birthweight group yielded similar results. Extubation failure was significantly lower in the smallest group, 500-750 grams.

In accordance with the core outcome set developed by Ringrow (13), the items HRQoL and LOS were not reported in the study by Hermeto (26).

Study quality graded with the QualSyst tool (15) 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 Gärtner (16) 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 (26). This study included a large group of neonates, its methodological quality was good, and the results were encouraging.

Barker (24, 25) performed a comparable study in a NICU population, the data of which were published as two 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 ($p=0.55$). 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 mechanical ventilation strategies can be applied (31). Currently volume targeted ventilation (VTV) is preferred compared with pressure limited ventilation (32). VTV 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 enable to 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 the use of supportive medication such as caffeine or steroids, indication for extubation, and post-extubation 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 paediatric ICUs in the UK is underway and is actively recruiting ~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 consultant of the medical library. The study selection was performed by several pairs separately. The quality of the manuscripts 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 could not provide any additional evidence. Only the large international search sites were screened; regional or national sites were not searched. Relevant studies in other languages than English might therefore have been missed.

Conclusion:

Due to a lack of studies there is no robust evidence to support or disprove the use of a weaning protocol for the discontinuation of mechanical ventilation in neonates. Only one study showed encouraging results, but a new study is underway. Studies particularly focused on neonates should be undertaken to provide specific guidance for neonatal clinicians.

Conflict of interest:

All authors declare having no conflict of interest.

References:

1. Dani C, Bresci C, Lista G, Martano C, Messina F, Migliori C, et al. Neonatal respiratory support strategies in the intensive care unit: an Italian survey. *Eur J Pediatr.* 2013;172(3):331-6. doi: 10.1007/s00431-012-1885-3.
2. Walsh MC, Morris BH, Wrage LA, Vohr BR, Poole WK, Tyson JE, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr.* 2005;146(6):798-804. doi: 10.1016/j.jpeds.2005.01.047.
3. Manley BJ, Doyle LW, Owen LS, Davis PG. Extubating Extremely Preterm Infants: Predictors of Success and Outcomes following Failure. *J Pediatr.* 2016;173:45-9. doi: 10.1016/j.jpeds.2016.02.016.
4. Al-Mandari H, Shalish W, Dempsey E, Keszler M, Davis PG, Sant'Anna G. International survey on periextubation practices in extremely preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 2015;100(5):F428-31. doi: 10.1136/archdischild-2015-308549.
5. Tume LN, Kneyber MC, Blackwood B, Rose L. Mechanical Ventilation, Weaning Practices, and Decision Making in European PICUs. *Pediatr Crit Care Med.* 2017;18(4):e182-e8. doi: 10.1097/pcc.0000000000001100.
6. Chatburn RL, Deem S. Respiratory controversies in the critical care setting. Should weaning protocols be used with all patients who receive mechanical ventilation? *Respir Care.* 2007;52(5):609-19; discussion 19-21.
7. Ellis SM, Dainty KN, Munro G, Scales DC. Use of mechanical ventilation protocols in intensive care units: a survey of current practice. *J Crit Care.* 2012;27(6):556-63. doi: 10.1016/j.jcrc.2012.04.021.
8. Blackwood B, Murray M, Chisakuta A, Cardwell CR, O'Halloran P. Protocolized versus non-protocolized weaning for reducing the duration of invasive mechanical ventilation in critically ill paediatric patients. *Cochrane Database Syst Rev.* 2013;(7):Cd009082. doi: 10.1002/14651858.CD009082.pub2.

- 253 9. Blackwood B, Alderdice F, Burns KE, Cardwell CR, Lavery G, O'Halloran P. Protocolized versus
254 non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult
255 patients. *Cochrane Database Syst Rev*. 2010;(5):Cd006904. doi: 10.1002/14651858.CD006904.pub2.
- 256 10. Shalish W, Anna GM. The use of mechanical ventilation protocols in Canadian neonatal intensive
257 care units. *Paediatr Child Health*. 2015;20(4):e13-9.
- 258 11. Wielenga JM, van den Hoogen A, van Zanten HA, Helder O, Bol B, Blackwood B. Protocolized
259 versus non-protocolized weaning for reducing the duration of invasive mechanical ventilation in
260 newborn infants. *Cochrane Database Syst Rev*. 2016;3:Cd011106. doi:
261 10.1002/14651858.CD011106.pub2.
- 262 12. <https://www.who.int/infant-newborn/en/>. WHO; 2018 [cited 2018 04-12]; Available from:
263 <https://www.who.int/infant-newborn/en/>.
- 264 13. Ringrow SM, McAuley DF, Clarke M, Marshall JC, Connolly B, Rose L, et al. A core outcome set
265 for mechanical ventilation trials: the Covent study. *Thorax*. 2017;72(suppl 3):1-278. doi:
266 10.1136/thoraxjnl-2017-210983.139
- 267 14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and
268 meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi:
269 10.1371/journal.pmed.1000097.
- 270 15. Kmet LM. Standard quality assessment criteria for evaluating primary research papers from a
271 variety of fields. In: Lee RCC, L.S., editor. Edmonton: Alberta Heritage Foundation for Medical Research
272 (AHFMR); 2004.
- 273 16. Gartner FR, Nieuwenhuijsen K, van Dijk FJ, Sluiter JK. The impact of common mental disorders
274 on the work functioning of nurses and allied health professionals: a systematic review. *Int J Nurs Stud*.
275 2010;47(8):1047-61. doi: 10.1016/j.ijnurstu.2010.03.013.

- 276 17. Carlo WA, Pacifico L, Chatburn RL, Fanaroff AA. Efficacy of computer-assisted management of
277 respiratory failure in neonates. *Pediatrics*. 1986;78(1):139-43.
- 278 18. Demaray W, Sittig SE. Ventilation for life. Ventilator weaning techniques, age-specific
279 experiences. *AARC TIMES*. 2007;31(9):14.
- 280 19. Jouvet PA, Payen V, Gauvin F, Emeriaud G, Lacroix J. Weaning children from mechanical
281 ventilation with a computer-driven protocol: a pilot trial. *Intensive Care Med*. 2013;39(5):919-25. doi:
282 10.1007/s00134-013-2837-8.
- 283 20. Keogh S, Courtney M, Coyer F. Weaning from ventilation in paediatric intensive care: an
284 intervention study. *Intensive Crit Care Nurs*. 2003;19(4):186-97.
- 285 21. Luyt K, Boyle B, Wright DE, Petros AJ. Compared with specialist registrars, experienced staff
286 nurses shorten the duration of weaning neonates from mechanical ventilation. *Pediatr Crit Care Med*.
287 2002;3(4):351-4. doi: 10.1097/01.pcc.0000031366.07233.91.
- 288 22. Sinha SK, Donn SM. Difficult extubation in babies receiving assisted mechanical ventilation.
289 *Archives of disease in childhood - Education & practice edition*. 2006;91(2):ep42.
- 290 23. West G, Pope A. Factors promoting successful extubation: An audit of planned extubations in
291 preterm infants following the implementation of nursing guidelines. *Journal of Neonatal Nursing*.
292 2010;16(6):267-73. doi: <https://doi.org/10.1016/j.jnn.2010.07.019>.
- 293 24. 2014 AP. Oral Abstracts. *Journal of Paediatrics and Child Health*. 2014;50:1-39. doi:
294 10.1111/jpc.12528.
- 295 25. Barker A SK, Halliday R. Poster Presentations Sunday 19Monday 20 April. *Journal of Paediatrics*
296 *and Child Health*. 2015;51:85-105. doi: 10.1111/jpc.12884_6.
- 297 26. Hermeto F, Bottino MN, Vaillancourt K, Sant'Anna GM. Implementation of a respiratory
298 therapist-driven protocol for neonatal ventilation: impact on the premature population. *Pediatrics*.
299 2009;123(5):e907-16. doi: 10.1542/peds.2008-1647.

- 300 27. Randolph AG, Wypij D, Venkataraman ST, Hanson JH, Gedeit RG, Meert KL, et al. Effect of
301 mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized
302 controlled trial. *Jama*. 2002;288(20):2561-8.
- 303 28. Restrepo RD, Fortenberry JD, Spainhour C, Stockwell J, Goodfellow LT. Protocol-driven ventilator
304 management in children: comparison to nonprotocol care. *J Intensive Care Med*. 2004;19(5):274-84. doi:
305 10.1177/0885066604267646.
- 306 29. Rushforth K. A randomised controlled trial of weaning from mechanical ventilation in paediatric
307 intensive care (PIC). Methodological and practical issues. *Intensive Crit Care Nurs*. 2005;21(2):76-86. doi:
308 10.1016/j.iccn.2004.07.009.
- 309 30. Schultz TR, Lin RJ, Watzman HM, Durning SM, Hales R, Woodson A, et al. Weaning children from
310 mechanical ventilation: a prospective randomized trial of protocol-directed versus physician-directed
311 weaning. *Respir Care*. 2001;46(8):772-82.
- 312 31. Keszler M. Mechanical ventilation strategies. *Semin Fetal Neonatal Med*. 2017;22(4):267-74. doi:
313 S1744-165X(17)30064-1 [pii]
314 10.1016/j.siny.2017.06.003.
- 315 32. Keszler M. Volume-targeted ventilation: one size does not fit all. Evidence-based
316 recommendations for successful use. *Arch Dis Child Fetal Neonatal Ed*. 2019;104(1):F108-F12. doi:
317 archdischild-2017-314734 [pii]
318 10.1136/archdischild-2017-314734.
- 319 33. Chawla S, Natarajan G, Gelmini M, Kazzi SN. Role of spontaneous breathing trial in predicting
320 successful extubation in premature infants. *Pediatr Pulmonol*. 2013;48(5):443-8. doi:
321 10.1002/ppul.22623.

- 322 34. Kamlin CO, Davis PG, Morley CJ. Predicting successful extubation of very low birthweight infants.
323 Arch Dis Child Fetal Neonatal Ed. 2006;91(3):F180-3. doi: 10.1136/adc.2005.081083.
- 324 35. Shalish W, Latremouille S, Papenburg J, Sant'Anna GM. Predictors of extubation readiness in
325 preterm infants: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2018. doi:
326 archdischild-2017-313878 [pii]
327 10.1136/archdischild-2017-313878.
- 328 36. Hummler H, Schulze A. New and alternative modes of mechanical ventilation in neonates. Semin
329 Fetal Neonatal Med. 2009;14(1):42-8. doi: 10.1016/j.siny.2008.08.006.
- 330 37. Stein H, Firestone K. Application of neurally adjusted ventilatory assist in neonates. Semin Fetal
331 Neonatal Med. 2014;19(1):60-9. doi: 10.1016/j.siny.2013.09.005.
- 332 38. Mhanna MJ, Iyer NP, Piraino S, Jain M. Respiratory severity score and extubation readiness in
333 very low birth weight infants. Pediatr Neonatol. 2017;58(6):523-8. doi: 10.1016/j.pedneo.2016.12.006.
- 334 39. Spasojevic S, Doronjski A. Risk factors associated with failure of extubation in very-low-birth-
335 weight newborns. J Matern Fetal Neonatal Med. 2018;31(3):300-4. doi:
336 10.1080/14767058.2017.1285884.
- 337 40. Ferguson KN, Roberts CT, Manley BJ, Davis PG. Interventions to Improve Rates of Successful
338 Extubation in Preterm Infants: A Systematic Review and Meta-analysis. JAMA Pediatr. 2017;171(2):165-
339 74. doi: 2588411 [pii]
340 10.1001/jamapediatrics.2016.3015.
- 341 41. Lemyre B, Davis PG, De Paoli AG, Kirpalani H. Nasal intermittent positive pressure ventilation
342 (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after
343 extubation. Cochrane Database Syst Rev. 2017;2:CD003212. doi: 10.1002/14651858.CD003212.pub3.

344

345

Table 1

Literature search , dd 18 January 2018

		Doubles excluded
Embase	1072	1052
Medline Ovid	596	116
Web-of-Science	436	115
Cochrane central	136	5
Scopus	1137	443
Cinahl	234	51
Google Scholar	200	171
ProQuest theses	59	58
clinical trials.gov	88	88
Total	3958	2099

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 Respirator 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)

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 Respirator 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* ADJ born*) OR neonat* OR infant* OR baby OR babies OR (month* ADJ3 age*) OR prematur* OR dysmatur*).ab,ti.)

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 Respirator 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

381 (MH “Practice Guidelines+” OR (protocol* OR guideline*)) AND (MH infant+ OR MH “Intensive Care,
 382 Neonatal+” OR (newborn* OR (new* N born*) OR neonat* OR infant* OR baby OR babies OR (month* N3 age*)
 383 OR prematur* OR dysmatur*))

384 **Cochrane central**

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

393 **Web-of-Science**

394 TS=(((extubat* OR detubat*)) OR (((((respirat* OR breathing OR airway*) NEAR/3 (movement* OR artificial*
 395 OR assisted OR pressure* OR support* OR mechanic*)) OR ventilat* OR Respirator OR Respirators)) AND
 396 (wean* OR liberat* OR withdraw*))) AND (((computer OR proportion*) NEAR/3 assist*) OR (automat* NEAR/3
 397 system*) OR (smart NEAR/3 care) OR smartcare OR automode OR (adaptive NEAR/3 (support* OR assist*)) OR
 398 (mandatory NEAR/3 minute*) OR (neurally NEAR/3 adjust*) OR nava OR (volume NEAR/3 support) OR
 399 (pressure NEAR/3 support) OR psv OR (high NEAR/3 frequenc*) OR hfov) OR ((protocol* OR guideline*)) AND
 400 ((newborn* OR (new* NEAR/1 born*) OR neonat* OR infant* OR baby OR babies OR (month* NEAR/3 age*)
 401 OR prematur* OR dysmatur*))

402 **Scopus**

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

410 **PubMed publisher**

411 (“Airway Extubation”[mh] OR (extubat*[tiab] OR detubat*[tiab])) OR “ventilator weaning”[mh] OR
 412 (“Respiration, Artificial”[mh] OR “Ventilators, Mechanical”[mh] OR (((respirat*[tiab] OR breathing OR
 413 airway*[tiab]) AND (movement*[tiab] OR artificial*[tiab] OR assisted OR pressure*[tiab] OR support*[tiab] OR
 414 mechanic*[tiab])) OR ventilat*[tiab] OR Respirator OR Respirators)) AND (wean*[tiab] OR liberat*[tiab] OR
 415 withdraw*[tiab])) AND (“Therapy, Computer-Assisted”[mh] OR “High-Frequency Ventilation”[mh] OR
 416 (((computer OR proportion*[tiab]) AND assist*[tiab]) OR (automat*[tiab] AND system*[tiab]) OR (smart AND
 417 care) OR smartcare OR automode OR (adaptive AND (support*[tiab] OR assist*[tiab])) OR (mandatory AND
 418 minute*[tiab]) OR (neurally AND adjust*[tiab]) OR nava OR (volume AND support) OR (pressure AND support)
 419 OR psv OR (high AND frequenc*[tiab]) OR hfov) OR (“Practice Guidelines as Topic”[mh] OR “Guidelines as
 420 Topic”[mh] OR (protocol*[tiab] OR guideline*[tiab])) AND (infant[mh] OR “Intensive Care, Neonatal”[mh] OR
 421 (newborn*[tiab] OR (new born*[tiab]) OR neonat*[tiab] OR infant*[tiab] OR baby OR babies OR (month*[tiab]
 422 AND age*[tiab]) OR prematur*[tiab] OR dysmatur*[tiab])) AND publisher[sb]

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

Proquest 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*))

clinical trials.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 Pediatric Society (1990 to present), and
- the Perinatal Society of Australian and New Zealand (1993 to present).

451 **Table 2**

452 Included articles after first screening:

Study: Author/ year	Reason for inclusion or exclusion	Inclusion/ exclusion
Barker, 2014	Abstract presented at the Perinatal Society of Australia & New-Zealand 2014. No full text article available. Single centre prospective non-blinded cohort study. NICU setting. 111 episodes, between January and October 2013. 30% of the population were weaned using a protocol. This resulted in a reduction of duration of 2.4 vs 3.5 days. <u>Request for the unpublished data from the authors</u>	Included
Barker, 2015	Abstract presented at the Perinatal Society of Australia & New-Zealand 2015. No full text article available. Single centre 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 mechanical of 1.9 vs 2.4 days ($p > 0.5$) <u>Request for the unpublished data from the authors</u>	Included
Carlo WA, 1980	Single centre cohort study. NICU population. A computer algorithm versus standard interpretation of arterial blood gas values. The effect on the correction of blood gas derangements was compared.	excluded
Demaray W, 2007	Review of weaning protocols in the adult and paediatric intensive care unit. Article could not be retrieved/ found at the journal's website	excluded
Hermeto, 2009	Retrospective study, new weaning protocol for neonatal population. Development of clinical weaning guidelines for respiratory therapists. A pretest, posttest, second posttest was measured; 93, 109, and 99 neonates were included. Time to first extubation was shortened (median 5, 1.5, 1.2 days) and duration of MV (18, 5 and 6 days respectively).	included
Jouvet, 2013	Abstract of oral presentation at the European Society of Paediatric and Neonatal Intensive Care 2013, on the evidence of using weaning protocols in the paediatric and adult ICU.	excluded
Keogh, 2003	Single centre intervention study, PICU population, no neonates included. Historic cohort versus prospective cohort, after implementing weaning guidelines. Both total ventilation time and length of stay were longer post-intervention (median difference: total ventilation time -15.8 hours, $P < 0.068$; and LOS -23.75 hours, $P < 0.088$).	excluded
Luyt, 2002	Single-centre prospective randomized controlled trial. NICU population. 50 neonates were included. Nurse versus 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); $p = 0.0458$. No comparison of protocolized versus non-protocolized weaning described.	excluded
Randolph, 2002	Multi-centre, randomized controlled trial 182 children admitted to the paediatric intensive care unit requiring ventilator support for more than 24 hours randomly assigned; 3 excluded, 179 analysed among whom 31 neonates <u>Request for the unpublished data from the authors</u>	included
Restrepo, 2004	Single-centre prospective cohort study. Use of a ventilator management protocol versus standard non protocol-based care on the duration of weaning time. Overall ventilator	excluded

	duration was not significantly different. Ventilator Management protocol patients had a shorter weaning time (17.5 hours; range, 1-181) than had non-protocol patients (35 hours; range, 0.5-377; P=0.005). PICU population, no neonates were included according to the authors. pre-test patient age median range 48 (0.5-216) months; post-test 19 (0.5-252)	
Rushfort, 2005	A single-centre randomized controlled trial to compare outcomes between medical-led and nurse-led (protocol-directed) weaning from mechanical ventilation in a PICU setting. Patient age was 2-7 weeks. No comparison between protocolized versus non-protocolized weaning was described. The study could draw conclusions because of recruitment problems.	excluded
Schultz TR, 2001	Single-centre, multi-unit, randomized controlled trial 223 children requiring intubation and mechanical ventilation; 4 did not reach study end point; 219 analysed, sample includes neonates Request for the unpublished data from the authors.	included
Sinha S, 2006	Describing two case studies of the weaning process in neonates. No protocol used.	excluded
West G, 2010	Retrospective audit in a single centre. NICU population. Extubation failure described in relation to the adherence of the nursing guidelines during this period.	excluded

453

454

Table 3

Rating article F. Hermeto: P. Mansvelt and JM. Wielenga

Table 1. Checklist for assessing the quality of quantitative studies

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			

Total 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

Figure 1: Study inclusion flowchart