Clinical practice Guide for the ventilation mechanical of the Newborn Infant

JUNTA DE ANDALUCIA

Servicio Andaluz de Salud
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CLINICAL PRACTICE GUIDE FOR THE MECHANICAL VENTILATION OF THE NEWBORN INFANT

NEONATOLOGY CLINICAL MANAGEMENT UNIT
VIRGEN DEL ROCÍO UNIVERSITY HOSPITAL
SERVICIO ANDALUZ DE SALUD

SHORT TITLE

"GUIDE FOR THE MECHANICAL VENTILATION OF THE NEWBORN INFANT"

The purpose of this guide is to help doctors to take decisions involving newborn infants requiring mechanical ventilation. It is not intended to be mandatory, or to replace the clinical judgement of a doctor caring for a specific patient.

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CONFLICT OF INTERESTS

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TABLE OF CONTENTS

LEVELS OF EVIDENCE AND DEGREES OF RECOMMENDATION

Scottish Intercollegiate Guidelines Network (SIGN) Tables

Levels of Evidence	
1++	High quality meta-analyses, systematic reviews of CCTs, or CCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews of CCTs, or CCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews or CCTs, or CCTs with a high risk of bias.
2++	High quality systematic reviews of case-control or cohort studies or high quality case-control or cohort studies with a very low risk of confounding or bias, and a high probability that the relationship is causal.
2+	Well conducted case-control or cohort studies with a low risk of confounding or bias, and a moderate probability that the relationship is causal.
2-	Case-control or cohort studies with a high risk of confounding bias, and a significant risk that the relationship is not causal.
3	Non-analytical studies, e.g. case reports, case series.
4	Expert opinion.

Degrees of recommendations	
A	At least one meta-analysis, systematic review of CCTs, or CCTs rated as 1++ directly applicable to the target population or a systematic review of CCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+.
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++.
D	Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+.

☑	Good clinical practice point based on clinical experience or the agreement of the work group.

ABBREVIATIONS

BPD: "Bronchopulmonary Dysplasia"

CCT: "Controlled Clinical Trial"

CMV: “Conventional Mechanical Ventilation”

CPAP: “Continuous Positive Airway Pressure”

CPD: “Chronic Pulmonary Disease”

CPR: "Cardiopulmonary resuscitation"

ECMO: “Extracorporeal Membrane Oxygenation”

Etv: “expiratory tidal Volume”

FiO_2: "Fraction of inspired Oxygen"

GA: "Gestational Age"

HFPPV: "High Frequency Positive Pressure Ventilation"

HFV: “High Frequency Ventilation”

iNO: “inhaled Nitric oxide”

IT: "Inspiratory Time"

IVH: “Intraventricular Haemorrhage”

MAP: “Mean Airway Pressure”

NICU: "Neonatal Intensive Care Unit"

OR: “Oxygenation Rate”

PC: “Pressure Control”

PEEP: "Positive End-Expiratory Pressure"

PIP: "Peak Inspiration Pressure"

PIV: "Patient Initiated Ventilation"

RDS: "Respiratory Distress Syndrome"

Rf: "Respiratory frequency"

SIMV: "Synchronized Intermittent Mandatory Ventilation"

Tv: “Tidal volume”

VC: “Volume Control”

KEY QUESTIONS TO ANSWER

1. In which clinical situations would starting mechanical ventilation not be indicated for a premature newborn infant with respiratory dysfunction who would generally be prescribed it?
2. In which clinical situations would initiating mechanical ventilation not be indicated for a term or near-term newborn with respiratory dysfunction who would generally be prescribed it?
3. Is the systematic intubation in the delivery room of premature babies born before 29 weeks more efficient in clinical terms than selective intubation?
4. In premature newborns with respiratory dysfunction requiring initiation of mechanical ventilation, is the application of high frequency ventilation (HFV) more efficient than conventional ventilation in clinical terms?
5. In term or near-term newborns with respiratory dysfunction requiring the initiation of mechanical ventilation, is HFV more efficient in clinical terms than conventional ventilation?
6. In premature newborns with severe respiratory dysfunction already on conventional mechanical ventilation (CMV), which is more efficient in clinical terms, maximising this or switching the patient to an equivalent high-frequency regime?
7. In term or near-term newborns with severe respiratory dysfunction already on CMV, which is more efficient in clinical terms, maximising this or switching the patient to an equivalent, high-frequency regime?
8. Which are the gasometric objectives of mechanical ventilation in the premature newborn?
9. Which are the gasometric objectives of mechanical ventilation in the term or near-term newborn?
10. In HFV, which is the most efficient frequency in clinical terms for the premature newborn?
11. In HFV, which is the most efficient frequency in clinical terms for the term or near-term newborn?
12. In HFV, what is the most efficient mean airway pressure (MAP) in clinical terms for the premature newborn?

13. In HFV, which is most efficient MAP in clinical terms for the term or near-term newborn?
14. In the premature newborn on conventional ventilation, above which MAP would a significant increase in clinically relevant complications be expected?
15. In term or near-term newborns on conventional ventilation, above which MAP would a significant increase in clinically relevant complications be expected?
16. During the CMV of the premature newborn, are there any clinically relevant differences between the routine use of sedation, no sedation or sedation on demand?
17. During the CMV in the term or near-term newborn, are there any clinically relevant differences between routine use of sedation, no sedation or sedation on demand?
18. During the CMV of the premature newborn, are there any clinically relevant differences between the routine use of the neuromuscular block, its non-use and its use on demand?
19. During the CMV of the term or near-term newborn, are there any clinically relevant differences between the routine use of neuromuscular block, its non-use and its use on demand?
20. Which is more efficient in clinical terms for the premature newborn, ventilation controlled by pressure or by volume?
21. Which is more efficient in clinical terms for term or near-term newborns - ventilation controlled by pressure or by volume?
22. When mechanical respiratory support is required for the newborn, which is more efficient in clinical terms, synchronised ventilation or conventional non-synchronised ventilation?
23. In the premature newborn on CMV to be withdrawn due to improvement, which is more efficient in clinical terms, extubation replaced by transitory nasal CPAP or not passing through this stage?
24. In the term or near term infant on CMV to be withdrawn due to improvement, which is more efficient in clinical terms, extubation to transitory nasal CPAP or continuing without this?
25. Are there any clinically relevant differences for the premature newborn, between direct extubation from the HFV and that carried out including an intermediate stage with conventional medication?
26. Are there any clinically relevant differences for the term or near-term newborn, between direct extubation from the HFV and that carried out including an intermediate stage of conventional medication?

SUMMARY OF THE RECOMMENDATIONS

D	Do not start mechanical ventilation in extremely premature babies being less than 23 weeks GA or weighing less than 400 grams at birth.
D	Start mechanical ventilation in extremely premature babies ≥ 25 weeks of GA, unless the foetus is evidently compromised by infection or hypoxia-ischemia
☑	In intermediate situations (≥ 23 and < of 25 weeks of GA), of uncertain prognosis, each case will be evaluated individually, taking into account, among other considerations, the parents' opinion and family history, being able to contemplate at any time the limitation of therapeutic efforts according to clinical evolution.
D	Do not start mechanical ventilation in newborns with anencephalic or confirmed chromosomal abnormalities incompatible with life, such as trisomy 13 or 18.
D	Do not start mechanical ventilation in newborns after having carried out continuous, appropriate resuscitation for ten minutes and no vital signs are present.
B	Systematic intubation in the delivery room is not recommended for premature babies with a GA younger than 29 weeks.
D	Resuscitation in the delivery room is recommended for all premature babies with a GA younger than 29 weeks using a CPAP/PEEP system that allows positive pressure to be applied to the airway. Intubation must be limited to those requiring it according to universally accepted resuscitation criteria.
B	Premature babies with a GA younger than 29 weeks who have received prenatal corticoids and who breathe spontaneously within five minutes of life can be managed safely and without needing intubation by the application of CPAP/PEEP, should they require support for respiratory distress.

A	In premature RDS requiring mechanical ventilation support, the prognosis at two years of age is not affected by whether conventional or high frequency ventilation is used.
B	If conventional ventilation is used, the pulmonary protection strategies on low Tv and high Rf have given the best results.
B	In respiratory dysfunction of term or near-term newborns requiring mechanical ventilation support, the short-term prognosis is not affected depending on whether conventional or high ventilation is used.
D	HFV may be a better alternative than CVM in the presurgical stabilisation of a herniated diaphragm.
D	There is no evidence that that HFV should be systematically recommended as a rescue technique in situations of severe respiratory dysfunction in premature newborn infants, although it could be beneficial in selected cases, particularly air leaks.
D	There is no evidence that that HFV should be systematically recommended as a rescue technique in situations of severe respiratory dysfunction in term or near-term newborn infants, although it could be beneficial in selected cases.
D	The generally accepted benchmark values in clinical practice establish a normocapnia in arterial blood of between 35-50 mmHg, and normoxemia between 50-60 mmHg for a premature newborn infant, and between 50-70 mmHg for a term or near-term newborn infant, always with a Ph of between 7.25 and 7.45.
B **D**	There is insufficient evidence for or against recommending routine “permissive hypercapnia”- defined with elevated $PaCO_2$ and Ph > 7.20- as a strategy to reduce mortality, respiratory morbidity or neurological development deficit. It is not possible to make recommendations based on CCT on the most efficient frequency of HFV to use, either in premature, term or near-term newborn infants. The "optimal" frequency in each case could be dependent on body weight, the mechanical characteristics of the lung, the device used and the ventilation strategy chosen.

D	It is not possible to make recommendations based on CCT on the most efficient pressure to use in high frequency ventilation, either in premature, term or near-term newborn infants. The "optimal" MAP to use in the HFV must be individualised in each case. (Grade D).
D	No threshold value for "safety" can be determined based on CCT in the MAP conventionally ventilated premature and term newborn infants, as exceeding these will significantly increase the appearance of clinically relevant complications. In moderate to severe respiratory function in a specific patient, it can be easier and safer to maintain optimal pulmonary expansion when ventilating with HFV than conventional.
☑	It is recommended that objective, reliable criteria be available to guide the transition from conventional to high frequency ventilation, in the event of moderate or severe respiratory dysfunction.
A	Systematic sedation of premature babies undergoing CMV with midazolan is not recommended. Its use in these circumstances is associated with relevant adverse effects, death, cerebral haemorrhage, periventricular leucomalacia, and it prolongs the stay in the NICU.
A	There is no evidence supporting the systematic use of opioids in premature newborns undergoing conventional mechanical ventilation.
B	Although there is no direct evidence in term newborn infants on CMV, or in the case of premature or term infants on HFV, the systematic use of sedation with midazolan or opioids is not recommended either.
☑	The occasional administration of drugs - benzodiazepines or opioids - is accepted for sedative purposes when patients are on mechanical ventilation. In these cases, it is recommended that a complete clinical evaluation first be made to detect ventilation problems - obstruction and/or incorrect positioning of the endotracheal tube - changes in the level of respiratory support based on the deterioration of the clinical situation or

	the appearance of complications - air leaks - and the need to adjust the ventilation regime. If the drug is eventually administered, it is recommended that clinical and gasometrical results be immediately evaluated.
D	The systematic use of neuromuscular blockers in premature newborn babies on mechanical ventilation is not recommended, although its occasional administration can prove beneficial in those breathing asynchronically with the respirator.
☑	There is no evidence derived from CCT, either for or against, regarding the use of neuromuscular blocks in term or near-term newborn infants on CMV, or patients receiving HFV. However, their possible beneficial effects are acknowledged when used together with sedatives, in clinical situations involving pulmonary hypertension.
A	In the RDS of premature newborn infants, mechanical ventilation in predefined or guaranteed mode - CV- is safe and efficient, meaning it could be an alternative to the pressure control mode.
B	There is no evidence deriving from CCT either for or against the use of predefined or guaranteed volume modes in term or near-term newborn infants. However, there are no barriers against extrapolating the positive effects achieved in premature infants with this mode.
A	In RDS of the premature newborn infant, high ventilation frequencies tend to achieve patient-machine synchronisation, and are preferable to low frequencies, below 60 per minute.
B	Amongst the synchronisation strategies, HFPPV seems to give better results in the RDS stage phase of the premature newborn infant, while PIV and SIMV would be preferred during weaning.
B	There is no evidence from CCT, either for or against, in term or near-term newborn groups, with regard to patient-respirator synchronisation strategies. Although there is nothing to prevent the extrapolation of the conclusions reached in premature infants

	with said strategies.
A	In newborn premature infants, the use of nasal CPAP is effective in the prevention of post-extubation respiratory failure, although it does not prevent reintubation or the need for oxygen at 28 days of life.
B	The majority of premature infants benefiting from nasal CPAP after extubation, weigh less than 1500 grams and receive, for a variable time, pressures equal to or higher than 5 cm of H_20.
☑	There is no evidence deriving from CCT that allows us to support or reject the systematic use of nasal CPAP in term or near-term newborns, as a strategy that facilitates respiratory stability after extubation. The work team considers that this group of newborn infants presents significant differences that prevent the extrapolation of the conclusion reached with the premature infants.
B	In premature newborn infants, direct extubation from HFV is possible and safe, and there is no need for an intermediate step through some kind of CMV.
C	The beneficial effects achieved with premature infants with transitory support using nasal postextubation CPAP from the CMV, can be extrapolated to the HFV situation.
C	Although there is no evidence to support any particular strategy as being more efficient for extubating the group of term or near-term newborn infants, there is nothing to prevent the extrapolation, in the same way as with the premature infants, that it is possible and safe to directly extubate them from HFV.

ABOUT THIS GUIDE

1. INTRODUCTION AND JUSTIFICATION

The application of mechanical ventilation as a support mechanism for respiratory function is one of modern medicine's great achievements in the care of critical patients. In the field of neonatology, its introduction has made a special contribution to the spectacular increase in survival in very premature infants and other pathologies affecting term newborn infants. However, it is a demanding procedure in terms of resources. To be used correctly, highly qualified staff and constant monitoring of vital signs are required, meaning this technique characterises and justifies the creation of intensive care units.

Although it has been empirically shown that this is a "life-saving" technique, it also causes potentially fatal iatrogeny. Severe episodes of hypoxemia with extreme bradicardy and/or cardiac arrest caused by undetected or inadequately treated ventilation problems, air leaks, pulmonary injuries associated to the use of ventilators, bronchopulmonary dysplasia (BPD) and associated pneumonia, are some of the collateral damage associated with the technique. All these adverse effects are multiplied when mechanical ventilation needs to be prolonged and/or intensified. This is why it is so important to use this life support treatment appropriately, optimising its indications and practical application.

In spite of the enormous experience gathered since its introduction, it is necessary to highlight here that there is a lack of clinical trials. It can therefore be confirmed in a generic manner, that the different modes or strategies with which mechanical ventilation is routinely applied have no other scientific support, in the best of cases, apart from animal experimentation, empiricism, or agreements reached at local level. In addition to this, the lack of published documentation capable of guiding the actions of doctors is surprising, the inevitable consequence of which is a great deal of variability in its clinical practice, not just among hospitals, but within the units themselves.

The creation of a guide to the mechanical ventilation of the newborn infant is, in our opinion, fully justified based on the following grounds:

- The practice of mechanical ventilation is a procedure sensitive to iatrogeny, and is therefore likely to improveme.

- This procedure is also a controversial matter among doctors, when it comes to deciding which ventilation strategies are the most appropriate, in terms of clinical efficacy, according to the different practical situations.

- The incorporation of new techniques such as nitrous oxide and the spread of others, such as high frequency ventilation (HFV) and extracorporeal membrane oxygenation (EMO), which have changed the way severe respiratory failure is managed.

- Impact on the most efficient management of the beds in the Neonatal Intensive Care Unit (NICU), both in terms of the magnitude of total hours of mechanical ventilation, and because it is a deciding factor in the mandatory care of these patients in these units. A priori, the efficient management of mechanical ventilation can lead to clinical benefits for the patients and for the institution itself, as it aims to improve its management.

- To do not know any quality Clinical Practice Guide and/or Protocols which can be adapted to the care we provide.

2. SCOPE AND OBJECTIVES

We have aimed to prepare some recommendations, based on the best available scientific evidence, for the correct practical application of mechanical ventilation in our unit. By extension, they could be useful to all doctors facing the daily task of ventilating newborn infants. We therefore set ourselves the following *OBJECTIVES*:

1. Adapting the indications for starting mechanical ventilation to the best scientific evidence available, as well as the different modes and strategies to be applied in each specific clinical situation.

2. Decreasing the variability in the practical application of mechanical ventilation among the healthcare personnel in the unit.

3. Decreasing the number of complications related to mechanical ventilation. In an operative mode, we pretend the following:

    a. Decreasing the frequency of air leaks.

    b. Decreasing the frequency of pneumonia associated to mechanical ventilation.

4. Decreasing the incidence of chronic pulmonary disease in newborns weighing less than 1500 g.

5. Optimising the duration of the mechanical ventilation decreasing the number of hours of mechanical ventilation per patient per year.

The CONTENTS we have taken into account are the following:

- Indications for initiating mechanical ventilation, as well as the most appropriate mode and strategy in the different clinical situations.

- Indications and action regimes for sedation and neuromuscular blocks in the application of mechanical ventilation.

- Recognising the clinical conditions in which it is possible to withdraw mechanical ventilation and the "*modus operandi*" for extubation.

- Prevention of the most frequent complications associated with mechanical ventilation.

This guide shall be applied to all neonatology patients in whom mechanical ventilation is indicated. Only those patients in whom it would formally be unethical to initiate any type of advanced life support have been excluded. It is conceived as a tool that will serve as a guide for making decisions for all medical personnel responsible for the care of these critical patients, but it is also aimed at achieving objective clinical objectives and resource management. Procedures such as endotracheal tube, correct fixing and maintenance, surveillance of mechanical ventilation and the aspiration of secretions, among others, which are usually carried out by nursing staff, have deliberately been excluded from this guide.

3. METHODOLOGY

We have started from the hypothesis that the drafting of a guide on mechanical ventilation should include the facts that provide the best available scientific evidence with local experience. This will be the most efficient way of making the adaptations necessary to these principles, for their subsequent application in our area. This is the reason why such considerable efforts have been made to gather and summarise this body of scientific evidence, for which the estimates of medicine based on the evidence of Sackett DL et al [1] have been adopted.

To summarise, the first relevant clinical decision-making points have been identified about which key questions have been prepared that can be answered. When asking these questions, the "PICO" scheme has been used, which involves the comparison of a variety of well-defined interventions, based on relevant clinical results on specific patients. The evidence available on each question has been summarised and classified according to reproducible criteria. From this synthesis, the recommendations that have been used as the basic pillars for the final drafting of the decision-making algorithms have been made, reserving the integration of the local experience as a modulating element of judgement. Clinical efficiency has been chosen as the determining criteria in the process of translating the evidence available to the specific recommendation.

The entire process was carried out by the work group formed for this purpose by doctors from the Neonatology Unit. The questions were distributed among all the group members to be answered in pairs, each member working independently. The pairs came to an agreement about an answer in the event of any discrepancies, always after a detailed discussion and with the participation of the coordinators. To establish the objectives, identify the relevant clinical decision-making points, draft the key questions and write the final guide, a group discussion method was used and agreement was sought.

This work group drafted the first document, which was submitted to external reviewers, neonatal doctors specialised in mechanical ventilation of new born infants. The considerations and suggestions made by these reviewers were then discussed in depth by the work group, and were eventually included in the final document.

3.1 Statement of relevant clinical questions

These were made by building a list of decisions often faced by doctors responsible for caring for newborn infants in different clinical settings, and which can be grouped according to the starting phases, maintenance and weaning from mechanical ventilation (Annex I).

1. In which clinical situation would starting mechanical ventilation not be indicated for a premature newborn infant with respiratory dysfunction in which we would generally prescribe it?
2. In which clinical situations would initiating mechanical ventilation not be indicated for a term or near-term newborn with respiratory dysfunction in which we would generally prescribe it?
3. Is the systematic intubation in the delivery room of premature babies born before 29 weeks more efficient in clinical terms than selective intubation?
4. In premature newborns with respiratory dysfunction requiring initiation of mechanical ventilation, is the application of high frequency ventilation (HFV) more efficient than conventional ventilation in clinical terms?
5. In term or near-term newborns with respiratory dysfunction requiring the initiation of mechanical ventilation, is HFV more efficient in clinical terms than conventional ventilation?
6. In premature newborns with severe respiratory dysfunction already on conventional mechanical ventilation (CMV), which is more efficient in clinical terms, maximising this or switching the patient to an equivalent, high-frequency regime?
7. In term or near-term newborns with severe respiratory dysfunction already on CMV, which is more efficient in clinical terms, maximising this or switching the patient to an equivalent, high-frequency regime?
8. What are the gasometric objectives of mechanical ventilation in the premature newborn?
9. What are the gasometric objectives of mechanical ventilation in the term or near-term newborn?
10. In HFV, which is most efficient in clinical terms for the premature newborn?
11. In HFV, which is most efficient in clinical terms for the term or near-term newborn?
12. In HFV, which is the most efficient MAP in clinical terms for the premature newborn?

13. In HFV, which is the most efficient MAP in clinical terms for the term or near-term newborn?
14. In the premature newborn on conventional ventilation, which is the MAP above which a significant increase in clinically relevant complications would be expected?
15. In term or near-term newborns on conventional ventilation, which is the MAP above which a significant increase in clinically relevant complications would be expected?
16. During the CMV of the premature newborn, are there any clinically relevant differences between the routine use of sedation, no sedation or sedation on demand?
17. During the CMV in the term or near-term newborn, are there any clinically relevant differences between routine use of sedation, no sedation or sedation on demand?
18. During the CMV of the premature newborn, are there any clinically relevant differences between the routine use of the neuromuscular block, its non-use and its use on demand?
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20. Which is more efficient in clinical terms for the premature newborn, ventilation controlled by pressure or by volume?
21. Which is more efficient in clinical terms for term or near-term newborns, ventilation controlled by pressure or by volume?
22. When mechanical respiratory support is required for the newborn, which is more efficient in clinical terms, synchronised ventilation or conventional non-synchronised ventilation?
23. In the premature newborn on CMV to be withdrawn due to improvement, which is more efficient in clinical terms, extubation replaced by transitory nasal CPAP or not passing through this stage?
24. In the term or near term infant on CMV to be withdrawn due to improvement, which is more efficient in clinical terms, extubation to transitory nasal CPAP or continuing without this?
25. Are there any clinically relevant differences for the premature newborn, between direct extubation from the HFV and that carried out including an intermediate stage with conventional medication?

26. Are there any clinically relevant differences for the term or near-term newborn, between direct extubation from the HFV and that carried out including an intermediate stage of conventional medication?

3.2 Bibliographical search

3.2.1 Search for possible clinical practice guides and/or protocols

Firstly, a search was made of any possible clinical practice guides or protocols for mechanical ventilation in neonatology. In order to do this, a search of the MEDLINE (PubMed) databases and TRIPDatabase was made using the key words "Mechanical Ventilation", "Assisted Ventilation" defining the type of study as "Practice Guideline" or "Systematic Reviews". The following were used: "Mechanical Ventilation" [MeSH] AND Guideline [TP]; "Assisted Ventilation" [MeSH] AND Guideline [TP]; use of methodology filter "Clinical Queries" for "Systematic Reviews"; Practice Guideline [TP] OR Guideline [TI*] AND "Mechanical Ventilation" [MeSH]; Practice Guideline [TP] OR Guideline [TI*] AND "Assisted Ventilation" [MeSH]. The search was also widened by including key terms such as "protocol*" [TI], "consensus" [TI], "recommended" [TI].

In a complementary manner, data bases from the following organisations that compile and/or prepare guides have been consulted: National Guideline Clearinghouse (http://www.guideline.gov/), CMBA INFOBASE http://www.mdm.ca/, National electronic Library for Health (NeLH) http://www.nelh.nhs.uk/guidelinesfinder/, Agency for Health Research and Quality (AHRQ) http://www.ahrq.gov/, GuiaSalud http://www.guiasalud.es/, American College of Physicians (ACP) http://www.acponline.org/, Institute for Clinical System Improvement (ICSI) health care guidelines http://www.icsi.org/, National Health and Medical Research Council (NHMRC) file:///htpp//www.hhmrc.gov.au, New Zealand Guidelines Group http://www.nzgg.org.nz/, Royal College of Physicians Guidelines (RCP) http://www.rcplondon.ac.uk/, Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/.

3.2.2 Bibliographical search regarding the questions asked

A search, with no time limit, was made to April 2008 in the MEDLINE (PubMed) and EMBASE data bases. To summarise, the terms MeSH ("Medical Subject Heading") were identified in each case and, based on these, the most detailed search strategy possible was created, limited by the term "newborn" and the methodological filter for the study type, when appropriate. The "Cochrane" database of systematic reviews was also investigated, as well as the clinical studies registered therein. Additionally, and based on the articles selected, a manual search was made of other relevant works mentioned in these.

3.3 Criteria for selecting articles and critical reading

When selecting the articles, Clinical Practice Guides, Systematic Revisions, Meta-analyses and controlled clinical trials (CCT) were first considered. In their absence, groups of studies and controlled cases, as well as case series were taken into account. Only studies performed in humans were selected. The articles on conference agreements, protocols for mechanical ventilation set out in the clinical trials and expert opinions have been used when no other evidence was available. Finally, if none of these were found, the group writing the guide has listed "good clinical practice points" based on the clinical experience of the group. All the articles selected have been individually evaluated by at least two members of the work group with the help of critical reading plans[2], and by the coordinators if they did not agree on the formers.

3.4 Levels of evidence and degrees of recommendation

The SIGN (Scottish Intercollegiate Guidelines Network) classifications have been used, which will be listed below[3].

Levels of Evidence	
1++	High quality meta-analyses, systematic reviews of CCTs, or CCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews of CCTs, or CCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews or CCTs, or CCTs with a high risk of bias.
2++	High quality systematic reviews of case-control or cohort studies, or high quality case-control or cohort studies with a very low risk of confounding or bias, and a high probability that the relationship is causal.
2+	Well conducted case-control or cohort studies with a low risk of confounding or bias, and a moderate probability that the relationship is causal.
2-	Case-control or cohort studies with a high risk of confounding or bias, and a significant risk that the relationship is not causal.
3	Non-analytic studies, e.g. case reports, case series.
4	Experts opinions.

Degrees of recommendations	
A	At least one meta-analysis, systematic review, or CCT rated as 1++ and directly applicable to the target population or a systematic review of CCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+.
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++.
D	Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+.

☑	Good clinical practice point based on clinical experience of the drafting group.

SUMMARY OF EVIDENCE

RECOMMENDATIONS

DECISIONS AT THE BEGINNING OF MECHANICAL VENTILATION

Question 1

In which clinical situation would starting mechanical ventilation not be indicated be for a premature newborn with respiratory dysfunction in which we would generally prescribe it?

We have considered this situation in the context of the neonatal cardiopulmonary resuscitation manoeuvres (CRM). There is international consensus expressed through the Work Group on Advanced Life Support of the International Liaison Committee on Resuscitation (ILCOR)[4]. This group is made up by the "American Heart Association", the "European Resuscitation Council", the "Australian Resuscitation Council", the "Heart and Stroke Foundation of Canada", the "Resuscitation Councils of Southern Africa" and the "Latin American Council on Resuscitation". These latter standards were published in November 2005, under a IIa recommendation (Acceptable and useful although not finally proven)[5,6] and recommend that extremely premature infants with a GA of fewer than 23 weeks or weighing less than 400 g at birth should not be resuscitated, and that it should be started at 25 weeks of GA or older without evident foetal comprise. It was also observed that the follow up of these guides must be interpreted in relation to the usual results in the region. This international consensus has been adopted by the Neonatal CPR Group of the Spanish Neonatology Society[7] (**Level of evidence 3-4**).

Recommendations

- *Do not initiate mechanical ventilation in extremely premature babies younger than 23 weeks of GA or weighing less than 400 g at birth. (Grade D)*
- *Initiate mechanical ventilation in extremely premature infants ≥ 25 weeks of GA, unless the foetus is evidently compromised by infection or hypoxia-ischemia. (Grade D)*

- *In intermediate situations (≥ 23 and < 25 weeks of GA), of uncertain prognosis, each case will be evaluated individually, taking into account, among other considerations, the parents' opinion and the family history, being able to contemplate at any time the limitation of therapeutic efforts according to clinical evolution. (☑)*

Question 2

In which clinical situations would initiating mechanical ventilation not be indicated for a term or near-term newborn with respiratory dysfunction in which we would generally prescribe it?

In the same way as for the pre-term infants, we have considered this situation as part of the neonatal resuscitation manoeuvres. There is also an international consensus expressed through the same ILCOR Work Group. The most recent standards were published in November 2005[4], and under the type II-a[5] recommendation, advising not to resuscitate newborns with anencephalic or confirmed chromosomal abnormalities incompatible with life, such as for example Trisomia 13 and 18. At the same time, and under the type II-b recommendation[8, 9], resuscitation is recommended to be withdrawn from the newborn without vital signs when continuous, adequate resuscitation has been given for ten minutes. This international consensus has been adopted by the Neonatal CPR Group of the Spanish Neonatology Society[7] (**Level of evidence 3-4**).

Recommendations

- *Do not initiate mechanical ventilation in newborns with anencephalic or confirmed chromosomal abnormalities incompatible with life, such as trisomy 13 or 18 (Grade D).*
- *Do not initiate mechanical ventilation in newborns not presenting vital signs after having carried out continuous, appropriate resuscitation for ten minutes. (Grade D)*

Question 3

Is the systematic intubation of premature newborns in the delivery room who were born at 29 weeks or younger more efficient in clinical terms than selective intubation?

There is no direct evidence in the current bibliography that the systematic intubation of the premature baby born at 29 weeks or younger is more efficient than the selective intubation in relation to morbidity and mortality of these and, at present, the subject of initial respiratory management in these newborns in the delivery room is a matter of controversy. After the initial substitutive administration of pulmonary surfactant for the prophylaxis of respiratory distress syndrome in the premature infant, different resuscitation routes have been used in the delivery room, which range from the systematic intubation of all premature infants of less than 29 weeks, to the administration of surfactant to selective intubation for those presenting respiratory distress, and the current preferences for intubation to administrate surfactant and rapid withdrawal of the ventilation, maintaining continuous positive pressure in the airway (CPAP), or the application from the first breaths of a CPAP to encourage alveolar distension. There is a Cochrane systematic review[10], although the studies included involve premature infants up to 35 weeks GA. Their conclusion is in favour of a strategy for the early administration of surfactant followed by a brief period of mechanical ventilation with subsequent support with CPAP, in the event of respiratory distress requiring oxygen therapy: A lower frequency of BPD or chronic pulmonary disease (CPD), with less need for mechanical ventilation, and also heavier consumption of surfactant (Level of evidence 1+). In a recent study comparing the strategy for applying from the delivery room CPAP-type respiratory support to infants under 28 weeks, and positive pressure ventilation using a mask with a "NeoPuff" device, which enables the operator to control the Peak Inspiration Pressure (PIP), pressure during expiration (PEEP) and the frequency of the ventilation, with a control group and without using intubation, unless indicated by reanimation criteria, it was seen that more than half did not require intubation in the delivery room and, when it was actually needed, this was inversely proportional to gestational age, furthermore, 20% of newborns did not require intubation during the first week of life[11] (**Level of evidence 1+)**. The COIN study (CPAP versus intubation at birth) was recently concluded and involved the recruitment of 610 subjects[12].

It has shown that half of the infants born at less than 29 weeks could be safely managed, although with a higher frequency of pneumothorax, with nasal CPAP without the need to intubate or administer surfactant, obtaining comparable results in terms of mortality and CPD in comparison to the group intubated at birth (Level of evidence 1+). It must be considered that this strategy can probably only be applied in newborns who have received prenatal corticoids and who breath spontaneously within five minutes of life, although they require some type of respiratory support, as occurred in this trial. The Neonatal CPR Group of the Spanish Neonatology Society[7] that recommends that all premature infants at 28 or fewer weeks of GA that do not require elective intubation in the delivery room must be resuscitated applying a CPAP/PEEP to prevent atelectrauma, provided that the resuscitation variables (heart rate, respiratory effort and colour) are positive (**Level of evidence 4**).

Recommendations

- *Systematic intubation in the delivery room is not recommended for premature babies with a GA of fewer than 29 weeks. (Grade B)*
- *Resuscitation in the delivery room is recommended for all premature babies born at 29 weeks or younger using a CPAP/PEEP system that allows positive pressure to be applied to the airway. Intubation must be limited to those requiring it according to universally accepted resuscitation criteria. (Grade D)*
- *Premature babies with a GA of below 29 weeks who have received prenatal corticoids and who breath spontaneously within five minutes of life can be managed safely and without needing intubation by the application of CPAP/PEEP, should they require support for respiratory distress. (Grade B)*

DECIDING STRATEGIES DURING MECHANICAL VENTILATION

Question 4

In premature newborns with respiratory dysfunction requiring initiation of mechanical ventilation, is the application of high frequency ventilation more efficient (HFV) than conventional ventilation in clinical terms?

There is a considerable body of evidence constituted by 18 CCT of acceptable quality that includes a total of 3801 subjects[13-30]. The majority of premature infants included were younger than 30 weeks GA that presented respiratory distress syndrome (RDS), and were ventilated with equipment fitted with an inspiratory branch oscillator, but differ in variables such as administration of surfactant, which was not done in the first three studies [13-15], when respiratory support was started, different high frequency ventilators – the Sensor Medic 3100 A was used in at least in 80% of the subjects - and ventilation strategies. The majority of the trials considered the mortality results, CPD, intraventricular haemorrhage brain injuries and periventricular leucomalacia evaluated by ultrasound. Only three studies have published neurodevelopment results[13, 27, 29.] These studies, with the exception of the latter, which was small in size[30], have been considered jointly in different meta-analyses and a Cochrane review [31-37] carried out during the last ten years.

There is strong, consistent evidence that HFV as opposed to conventional ventilation does not impact mortality (**Level of evidence 1++**). HFV showed a slight reduction in CPD in the first studies, which has been inconsistent with later studies and is not significant overall (**Level of evidence 1+)**. Through a cumulative and recurrent analysis carried out in two recent meta-analyses[36,37], it has been possible to show that both the use of surfactant and the choice of strategies for pulmonary protection in conventional mechanical ventilation, moderated the relative benefit attributed to the HFV in the first trials with regard to reduction of CPD, in such a manner that this supposed benefit disappeared when convention ventilation was optimised. Indeed, in studies using CMV strategies consisting of low tidal volumes (Tv) (< 6 ml/Kg)[24,25], or high respiratory frequencies, (Rf) (≥ 60/minute)[22,26,28], no differences were seen in the frequency

of CPD (Level of evidence 1+). Air leaks occurred more frequently with the HFV, this adverse effect appearing in one of every ventilated 26 patients (**Level of evidence 1+**).

The initial ventilation mode in premature infants, whether CMV of HFV, has no impact on morbidity in neurodevelopment (**Level of evidence 1+**). One of the first studies showed a higher incidence of deficit in the neurodevelopment associated with higher frequency of cerebral haemorrhage grade 3-4 in the HFV group[38], but was inconsistent in subsequent studies in which this high volume ventilation strategy was used[37].

Recommendations

- *In RDS in premature intants requiring mechanical ventilation support, the prognosis at two years of age is not affected by whether conventional or high frequency ventilation is used. (Grade A)*
- *When conventional ventilation is used, low Tv and high Rf pulmonary protection strategies have given the best results. (Grade B)*

Question 5

In term or near-term newborn infants presenting respiratory dysfunction and requiring starting mechanical ventilation, is HFV more efficient in clinical terms than CMV?

Only one CCT has been found that compares HFV and CMV as the first choice for respiratory dysfunction in term or near-term newborns[39]. In a small, multi-centre study, the causes of the respiratory dysfunction in 84% of the patients included was parenchymatous pulmonary disease, sepsis, and/or pneumonia, and no differences were seen in relevant clinical results, although some degree of contamination was seen in the high frequency group (**Level of evidence 1+)**.

Observations of case series with diaphragmatic hernia show a beneficial effect, based on historical controls, when high frequency was used in pre-operative stabilisation[40,41] (**Level of evidence 3)**. There is no evidence in humans supporting the use of HFV as the first choice in meconium aspiration syndrome (MAS).

Recommendations

- *In respiratory dysfunction of term or near-term newborns requiring mechanical ventilation support, short-term prognosis is not affected according to whether conventional or high ventilation is used. (Grade B)*
- *HFV may be a better alternative than CVM for the pre-surgical stabilisation of a herniated diaphragm. (Grade D)*

Question 6

In premature newborn infants with severe respiratory dysfunction already on conventional mechanical ventilation (CMV), which is more efficient in clinical terms, maximising this or switching the patient to an equivalent, high-frequency regime?

There is a lack of evidence supporting the use of HFV as an efficient measure in the situation of severe, complicated respiratory dysfunction of a premature newborn baby, such as interstitial emphysema. This is the conclusion of a Cochrane systematic review[42], in which only one small study could be included, performed in the era prior to the systematic use of surfactant, using a jet-type ventilator and without including evaluation of neurodevelopment [43] (**Level of evidence 1-).** Furthermore, there are observations of case series in which the HFV has been successfully used as a rescue technique (**Level of evidence 3)**.

Recommendations

There is no evidence that HFV should be systematically recommended as a rescue technique in situations of severe respiratory dysfunction in premature newborn infants, although it could be beneficial in selected cases, particularly air leaks. (Grade D)

Question 7

In term or near-term newborns with severe respiratory dysfunction already on CMV, which is more efficient in clinical terms, maximising this or switching the patient to an equivalent, high-frequency regime?

There is no data derived from CCT supporting the systematic use of HFV as a rescue strategy in severe respiratory failure in the term or near-term newborn infant[44]. Only one study has been found, which has methodological problems that did not show differences between conventional ventilation and high frequency ventilation[45] (**Level of evidence 1-**). Experience derived from case series, and epidemiological data indicating a decrease in the number of newborns receiving extracorporeal membrane oxygenation (EMO) because of respiratory failure[46], coinciding with the introduction of rescue techniques which include inhaled nitric oxide and HFV, do not enable the possible beneficial effect of this method of ventilator support to be ruled out on some patients' respiratory status (**Level of evidence 3**).

Recommendations

There is no evidence that HFV should be systematically recommended as a rescue technique in situations of severe respiratory dysfunction in term or near-term newborn infants, although it could be beneficial in selected cases.

Questions 8 and 9

- ***Which are the gasometric objectives of mechanical ventilation in the premature newborn?***
- ***Which are the gasometric objectives of mechanical ventilation in the term or near-term newborn?***

There are no data deriving from CCT directly supporting gasometric objectives in mechanical ventilation in the premature newborn infant, or in the term or near-term newborn infant. The experience gathered, mainly from numerous trials conducted for different purposes in different neonatal intensive care units, and the opinion of experts[16-18, 30, 39], establishes, homogenously and in the majority of cases, arterial blood gases for normocapnia of around 35-50mmHg, with a pH value between 7.25-7.45; and considers higher levels of $PaCO_2$ as "permissive hypercapnia", all with pH > 7.20. In the same way, the normoxemia values of PaO_2 in pre-term newborns is set at between 50-60 mmHg in arterial blood, and for term newborns between 50-70 mmHg (**Level of evidence 4**).

In relation to permissive hypercapnia as a protective pulmonary strategy during mechanical ventilation, there is a Cochrane systematic review[47] that analyses two controlled trials[48, 49]. From this evidence, gathered from a total of 269 premature newborn infants, most of whom weighed below 1000 g, no overall benefit can be inferred for permissive hypercapnia, although the need for more research is acknowledged (**Level of evidence** 1+). It must also be taken into account that these studies do not contribute data relating to neurodevelopment, which means there are doubts regarding the "safe" level for the $PaCO_2$. The ideal range for the aforementioned $PaCO_2$ in premature infants has not been determined, especially in term newborn infants, if such a range exists. It may not be the same for all newborn infants, but could also vary according to birth weight and/or GA (**Level of evidence 3-4**).

Recommendations

- *The generally accepted benchmark values in clinical practice establish arterial blood normocapnia of between 35-50 mmHg, and normoxemia between 50-60mmHg for a premature newborn infant, and between 50-70 mmHg for a term or near-term infant, all with a Ph of between 7.25 and 7.45.*
- *There is not enough evidence either for or against, to recommend routine "permissive hypercapnia"- defined as with elevated PaCO2 and Ph > 7.20- as a strategy for reducing mortality, respiratory morbidity or neurological development deficit. (Grade B*

Questions 10 and 11

- ***In HFV, which is the most efficient frequency in clinical terms for the premature newborn?***
- ***In HFV, which is the most efficient frequency in clinical terms for the term or near-term newborn?***

There is no data deriving from the CCT supporting one or the other as the most efficient frequency to be used neither in premature newborn infants nor in term or near-term infants, when they are ventilated with high frequency. However, there is considerable experience, and also an implicit or explicit agreement among experts, with regard to the practical application of protocols for this method of ventilation[13-28, 39, 40, 43, 45, 50-52] (**Level of Evidence 4**). Thus, in HFV the frequency can be very variable, with ranges between 4 and 28 Hz, also depending on the device used, but frequencies lower than 4 Hz or higher than15 Hz are rarely used. In general, the heavier the patient, the lower the frequency used, suggesting that in the very low-weight newborn infants - less than 1500 grams- starting with 15 Hz and in those weighing more, with 10 Hz, making adjustments as required to improve ventilation once the amplitude is maximised. Furthermore, according to the ventilator type used, the use of certain "standard" frequencies is recommended. For example, in the Sensor Medics 3.100A oscillator, the recommended frequency for a pre-term newborn of very low weight is 15 Hz and for a term or near-term infant

it is 10 Hz. In any case, it is thought that the theoretical benefits of HFV are due to its capacity to achieve a good gaseous exchange with small Tv, meaning there are grounds for using higher frequencies that enable appropriate gas transport.

Recommendations

It is not possible to make recommendations based on CCT on the most efficient frequency to use in the HFV, either in premature, term or near-term newborn infants. The "optimal" frequency in each case could be dependent on body weight, the mechanical characteristics of the lung, the device used and the ventilation strategy chosen. (Grade D)

Questions 12 and 13

- ***In HFV, which is the most efficient MAP in clinical terms for the premature newborn infant?***
- ***In HFV, which is the most efficient MAP in clinical terms for the term or near-term newborn?***

There is no reliable evidence available from CCT for establishing an "optimal" MAP in the HFV. In the same way as for the ventilation frequency, there is a extensive body of experienced based mainly on physiopathological concepts and expert opinion[13-28,39,40,43,45,50-52] (**Level of Evidence 4**). This is the main evidence that supports the practical management of the HFV in neonatal units.

The most efficient pressure is that average pressure required for obtaining and maintaining alveolar recruitment that permits adequate oxygenation with the inspired oxygen fracture (FiO_2) lower or equal to 0.6, preventing atelectrauma at the same time. It is usually possible to achieve increases of 1 to 2 cm H_2O until satisfactory oxygenation and/or evidence in the thoracic radiography of pulmonary hyperinsufflation, as may be suggested by flattening of the diaphragm and/or visualisation or more than nine intercostals spaces or eight in the case of the existence of air leaks.

There is no predetermined average level of pressure in the airway that must not be exceeded, as this depends on the mechanical properties of the lung, and is extremely variable for each patient on treatment. Inversely, there is no predetermined level of average pressure that must necessarily be maintained, especially if it causes a hemodynamic commitment and neither has it been shown that there is an improvement in the pulmonary ventilation and/or gaseous exchange. One of the greatest challenges facing doctors when ventilating a patient with HFV is to try and maintain a satisfactory or optimum pulmonary volume within the narrow margin that tends to exist between atelectasia and overdistenson of the lung, all taking place in changing conditions according to the different phases of the underlying pathological process. Thoracic radiography has been shown to be the most widely used method for evaluating the level of pulmonary insufflations, although it is also acknowledged that this is not the ideal method.

Recommendations

It is not possible to make recommendations based on CCT on the most efficient average pressure to use in the high frequency ventilation, either in premature, term or near-term newborn infants. The "optimal" MAP to use in the HFV must be customised in each case. (Grade D)

Questions 14 and 15

- ***In the premature newborn on conventional ventilation, which is the MAP above which a significant increase in clinically relevant complications might be expected?***

- ***In the term or near-term newborns on conventional ventilation, which is the MAP above which a significant increase in clinically relevant complications might be expected?***

No evidence can be extracted from CCT that allows a clear strategy to be established to avoid pulmonary damage induced by mechanical ventilation[50-54]. Experimental studies carried out in animals support the concept that pulmonary lesions induced by ventilation can be caused

by mechanical force which triggers an inflammatory reaction[55]. It would appear that such damages occur when there is some degree of pulmonary overdistension, which could make the final inspiration volume more important and, in consequence, the pressure dynamics which determine it - PIP, MAP and PEEP. HFV is proposed as a protective ventilation strategy because it leads to constant alveolar distension, avoiding atelectrauma, and adequate ventilation with low Tv. Although intensive clinical investigation has failed to show any clear benefits in respiratory distress in premature infants[13-37], the physiological concepts for protecting the lung derived from this have been applied in HFV strategies. Therefore, ventilation guided by low Tv to a sufficient PEEP to avoid atelectrauma have been adopted[25,26]. In addition to this, in selected cases such as severe respiratory failure, it is thought that HFV may provide the most efficient pulmonary protection[46], which is why the great majority of neonatal units have protocolised criteria for making the transition from conventional ventilation. These criteria vary from centre to centre, but also usually include a combination of oxygen requirements and the pressure necessary to maintain adequate pulmonary expansion and CO_2 elimination. In addition to this, the expected benefits should be optimised if HFV is started in not severe cases of respiratory failure, when the conclusion has been reached that this is the best way of maintaining alveolar recruitment at lower risk of barotrauma (**Level of evidence 3-4**).

Recommendations

- *No threshold value for "safety" based on CCT can be determined in the MAP applied to conventionally ventilated premature newborns and term newborns, meaning that, exceeding this value, the appearance of clinically relevant complications increases significantly. In moderate to severe respiratory function in a specific patient, it can be easier and safer to maintain optimal pulmonary expansion when ventilating with HFV than CMV. (Grade D)*
- *It is recommended that objective, reliable criteria be available to guide the transition from conventional to high frequency ventilation, in the event of moderate or severe respiratory dysfunction.* (☑)

Question 16 and 17

- ***During CMV of the premature newborn infant, are there any clinically relevant differences between the routine use of sedation, no sedation or sedation on demand?***
- ***During the CMV of the term or near-term newborn infant, are there any clinically relevant differences between the routine use of sedation, no sedation or sedation on demand?***

There are two "Cochrane" databases considering the topic of sedation and/or analgesics administered during mechanical ventilation of the newborn infant[56, 57]. The first focuses on the use of an intravenous infusion of midazolan[56], and analysed three clinical trials with a total of 148 newborn infants with a GA of less than 33 weeks or lower than 2000 g in weight[58-60], all on CMV. One study compared midazolan with placebo or morphine[58], observing a significant increase in adverse effects – death, severe cerebral haemorrhage or periventricular leucomalacia - in the midazolan group; furthermore, a meta-analysis of the other two studies included that compared midazolan with placebo[59, 60], observed a longer stay in the NICU than in the intervention group. The review concludes that there is no evidence supporting the use of midazolan for sedative purposes in premature infants during the stay in the NICU, and also presents doubts about its safety[56] (**Level of evidence 1+)**.

The second Cochrane[57] study reviewed the use of opioids during the CMV. It considered a total of 13 studies[60-73] with a total of 1505 children, mostly under 33 weeks, among whom a large multi-centre study including 898 subjects and compared morphine with placebo[62]. It concludes that there is insufficient data to recommend the routine use of opiates in newborn infants on mechanical ventilation, although it alleviates pain in a variable manner, it is neither worse nor better than other drugs or placebo in terms of clinical efficacy (**Level of evidence 1+**).

There are no data deriving from clinical trials that have evaluated the use of routine sedation with opioids or midazolan in conventionally ventilated term infants, or the use of HFV, both in premature and term newborn infants.

Recommendations

- *Systematic sedation of premature babies undergoing CMV with midazolan is not recommended. Its use under these circumstances is associated with serious adverse effects - death, cerebral haemorrhage, periventricular leucomalacia - and it lengthens the stay in the NICU. (Grade A)*
- *There is no evidence supporting the systematic use of opioids in premature newborns undergoing conventional mechanical ventilation. (Grade A)*
- *Although there is no direct evidence in term newborn infants undergoing CMV, or in the case of premature or term infants on HFV, the systematic use of sedation with midazolan or opioids is not recommended. (Grade B)*
- *The occasional administration of drugs - benzodiazepines or opioids - is acceptable for the purpose of sedating patients on mechanical ventilation. In these cases, it is recommended that a complete clinical evaluation first be made to detect ventilation problems - obstruction and/or incorrect positioning of the endotracheal tube - changes in the level of respiratory support based on the worsening of the clinical situation or the appearance of complications - air leaks - and the need to adjust the ventilation regime. If the drug is eventually administered, it is recommended that clinical and gasometric results be immediately evaluated.* (☑)

Question 18 and 19

- ***During the CMV of the premature newborn, are there any clinically relevant differences between the routine use of the neuromuscular block, its non-use and its use on demand?***
- ***During the CMV of the term or near-term newborn, are there any clinically relevant differences between the routine use of neuromuscular block, its non-use and its use on demand?***

A recent Cochrane review[74] included six CCT[75-80] comparing the systematic use of neuromuscular blocks with pancuronium during mechanical ventilation, with selective paralysis

and the non-use of neuromuscular paralysis in premature infants. There are not data deriving from clinical trials regarding term infants or those in whom pancuronium or other neuromuscular blocking agents are used. A total of 486 subjects were considered, all of whom were under 34 weeks and who received mechanical ventilation by RDS. The majority of the studies assess the mortality result, the incidence of the air leak syndrome, CPD and HIV. The results of pulmonary function and long-term neurodevelopment were not taken into account for none of these.

From the meta-analysis of those studies, it is concluded that the selective use of neuromuscular block with pancuronium in patients presenting asynchronous respiration with the respirator, produces a significant reduction in the frequency of IVH and air leak syndromes. These differences are not observed with the systematic use of neuromuscular blocking agents. There are no results regarding pulmonary function or regarding long-term neurological development, or the risks associated to its prolonged use.

The external validity of these studies is limited. Only one of these includes the use of a surfactant for the treatment of the RDS and only one involves the systematic use of sedation in the control group. The results of these studies cannot be totally extrapolated to our usual clinical practice (**Level of evidence 1-**). Currently, the generalisation of practices, such as the administration of prenatal corticoids, surfactant, synchronised modalities available in the most modern respirators, as well as the occasional administration of analgesics and sedatives, all have a positive effect on the evolution of ventilated newborn infants, considered both individually and as a group.

Recommendations

- *The systematic use of neuromuscular blockers in premature newborn babies receiving mechanical ventilation is not recommended, although its occasional administration can prove beneficial in those breathing asynchronically with the respirator. (Grade D)*
- *There is no evidence derived from CCT, either for or against, regarding the use of neuromuscular blocks in term or near-term newborn infants on CMV, or patients receiving HFV. However, their possible beneficial effects are acknowledged when used together with sedatives, in clinical situations involving pulmonary hypertension.* (☑)

Question 20 and 21

- ***Which is more efficient in clinical terms for the premature newborn: ventilation controlled by pressure or by volume?***
- ***Which is more efficient in clinical terms for the term or near-term newborns: ventilation controlled by pressure or by volume?***

There are nine CCT that compare assisted respiration with time limited cycle pressure with a controlled volume mode (CV). Of the nine clinical trials, eight have been considered jointly in the Cochrane review[81-85]. The other clinical trial has recently been published[86]. All the subjects in the five CCT finally analysed were 287 premature newborns. The majority of the studies have included premature infants younger than 34 weeks of GA. There are no significant differences in the studies with regard to the use of prenatal maternal steroids neither of surfactant in newborn infants. The carers were not blinded, nor were the results of the trials evaluated, except in one case. The majority of the studies have considered the results for mortality, CPD, HIV, duration of respiratory care and the pneumothorax rate. There are no data on the results on growth, long-term neurological development or death after release from hospital.

The use of respiratory care strategies with some type of CV - predefined or guaranteed volume- is a safe, efficient method in premature newborn infants, those of very low weight and extremely low weight when born with RDS (**Level of evidence 1+**). There are no significant differences with regard to mortality on release from hospital between the groups with respiratory care with CV and with pressure-limited, time-cycled ventilation (**Level of evidence 1++**). Although the reduction of the BPD borders statistical significance, other effects clearly benefiting the predefined volume group are clearly seen. These benefits lead to a reduction in the duration of the assisted respiration, the rate of severe pneumothorax and IVH (Grade III-IV) (**Level of evidence 1+)**. A trend to earlier extubation in premature newborn infants is also observed in cases with volume guarantee, which is significant in those weighing less than 1000 grams (**Level of evidence 1+**). In spite of the advantages found, these must be treated with caution, given the small number of newborn infants included in this analysis. Furthermore, two other studies show contradictory results[87,88]. These compare the efficacy of a volume guarantee mode in one case,

and regulated pressure CV in the other, with a synchronised pressure limited mode, without any evidence of differences in either of the two studies with regard to time of extubation or mortality between either modality (**Level 1+ of evidence**).

There is no data deriving from CCT in term or near term newborn infants, comparing the use of assisted respiration by way of Pressure-limited, time-cycled pulmonary ventilation with another non-guaranteed volume modality.

Recommendations

- *In the RDS of the premature newborn infant, predefined or guaranteed mode mechanical ventilation – CV - is safe and efficient, meaning it could be an alternative to the pressure control mode (Grade A).*
- *There is no evidence deriving from CCT either for or against the use of predefined or guaranteed volume mechanical ventilation modes in term or near-term newborn infants. However, there is no reason why the positive effects achieved in premature infants with this mode should not be extrapolated. (Grade B)*

Question 22

When mechanical respiratory support is required for the newborn, which is more efficient in clinical terms, synchronised ventilation or conventional non-synchronised ventilation?

It is a well-documented fact that the majority of mechanically ventilated newborn infants take spontaneous breaths. It is thought that synchronising the patient's respiratory efforts with the inspiration phase of the respirator makes a correct gaseous interchange possible, with lower pressures in the airway, which reduces the risk of barotrauma and consequentially complications from air leaks and pulmonary damages induced by mechanical ventilation. A total of 11 clinical studies[89-99] were recovered and analysed jointly by a Cochrane review[100]. These studies attempted to achieve patient-machine synchronisation by different strategies - high frequency positive pressure ventilation (HFPPV), patient initiated ventilation (PIV) and synchronised intermittent

mandatory ventilation (SIMV) - although none of these provided proof that this objective had been achieved. All the studies were conducted on premature babies presenting RDS. The HFPPV strategy against the CMV resulted in a lower incidence in air leaks, and the PIV/SIMV in a reduction of the mechanical ventilation period; none of these are associated with differences in respiratory or neurological mortality or morbidity, although a non-significant trend was seen for lower mortality with the HFPPV strategy versus CMV and towards higher mortality with PIV versus SIMV. PIV compared with SIMV was associated with a shorter weaning phase (**Level of evidence 1+)**.

There is no evidence drawn from clinical trials on which to base a definitive decision on any particular strategy for patient-machine synchronisation, when a term or near-term newborn infant is mechanically ventilated, although the conclusions in premature newborns could be extrapolated.

Recommendations

- *In RDS of the premature newborn infant, high ventilation frequencies tend to achieve patient-machine synchronisation, and are preferable to low frequencies, below 60 per minute. (Grade A)*
- *Among the synchronisation strategies, HFPPV seems to give better results in the RDS stage of the premature newborn infant, while PIV and SIMV would be preferred during weaning. (Grade B)*
- *There is no evidence from CCT, either for or against, in the term or near-term newborn groups, with regard to patient-respirator synchronisation strategies. However, the conclusions reached in premature infants treated with said strategies could be extrapolated. (Grade B)*

ABOUT WEANING FROM MECHANICAL VENTILATION

Questions 23 and 24

- ***In the premature newborn on CMV to be weaned due to recovery, which is more efficient in clinical terms: extubation replaced by transitory nasal CPAP or not passing through this stage?***
- ***In the term or near-term newborn infant on CMV to be weaned due to recovery, which is more efficient in clinical terms: extubation to transitory nasal CPAP or not passing through this stage?***

There are eleven CCT comparing extubation passing through transitory support with nasal CPAP against extubation without this. Of these eleven studies, ten have been analysed jointly in a Cochrane review[100-110], the other two being excluded for methodological reasons. The total number of subjects from the nine clinical trials finally analysed is 823 newborn infants. The majority of the premature infants included were below 1500 grams in weight, and the results of the failure of extubation because of respiratory failure have been considered - as defined by the presence of respiratory acidosis, an increase in oxygen requirements and/or frequent or severe apnoea - the need for endotracheal reintubation and the need for oxygen at 28 days of life.

Nasal CPAP is effective in the prevention of respiratory failure - presence of respiratory acidosis, increased oxygen requirements or frequent or severe apnoea - in premature newborn infants after extubation (**Level of efficacy 1++**). However, there are no significant differences in the reintubation figures or in the oxygen requirements at 28 days of life (**Level of efficacy 1++**).

In the case of term or near-term newborn infants, there are no data deriving from controlled clinical trials that support the decision to use nasal CPAP as a systematic strategy to facilitate respiratory stability after intubation.

Recommendations

- *In newborn premature infants, the use of nasal CPAP is effective in the prevention of post-extubation respiratory failure, although it does not prevent reintubation or the need for oxygen at 28 days of life. (Grade A)*
- *The majority of premature infants benefiting from nasal CPAP after extubation weigh less than 1500 grams and receive this during a variable time at pressures equal to or higher than 5 cm of H_20. (Grade B)*
- *There is no evidence from the CCT enabling us to support or reject the systematic use of nasal CPAP in term or near-term newborns, as a strategy to facilitate respiratory stability after extubation. The work team considers that this group of newborn infants presents significant differences that prevent the extrapolation of the conclusion reached with the premature infants. (☑)*

Questions 25 and 26

- ***Are there any clinically relevant differences for the premature newborn between direct extubation from the HFV and that carried out including an intermediate period of conventional medication?***
- ***Are there any clinically relevant differences for the term or near-term newborn between direct extubation from the HFV and that carried out including an intermediate period of conventional medication?***

There are no data deriving from CCT that compare direct extubation from HFV with extubation with an intermediate period of conventional ventilation. However, there is a great deal of experience derived from the studies designed to control HFV and CMV as the ventilation strategy of choice in cases of respiratory distress in premature infants[13-30], the majority of which do not permit the change from HFV to CMV at the time of weaning from the respirator, which can be analysed as a group ventilated with HFV. In fact, these studies have proven that direct extubation from HFV is possible and safe (**Level of evidence 2++**).

In the group of term or near-term newborn infants under HFV, no clinical trials supported a more efficient weaning system. *A priori*, the conclusions drawn from these premature infants could be extrapolated (**Level of evidence 2++**), as shown in a series of cases[111].

Recommendations

- *In premature newborn infants, direct extubation from the HFV is possible and safe, and there is no need for an intermediate step involving some kind of CMV. (Grade B)*
- *The beneficial effects achieved with premature infants receiving transitory support from CPAP nasal postextubation from the CMV, can be extrapolated to the HFV situation.*
- *Although there is no evidence to support any particular strategy as being more efficient for extubating the group of term or near-term newborn infants, there is nothing to prevent the extrapolation, so in the same way as with the premature infants it is possible and safe to directly extubate them from HFV. (Grade C)*

DIFFUSION, IMPLANTATION AND EVALUATION

A priori, there appears to be no significant barriers that help putting the recommendations formulated herein into practice. Indeed, this is the main conclusion of the trial phase carried out at our hospital which tends to detect possible difficulties in its generalised implantation. However, some practical considerations should be taken into account for their application in local areas.

1. Material and structural resources:
   - It is necessary to install oxymetres in delivery rooms to enable CRM to be practiced with the necessary oxygen in the 0.21-1 range.
   - Systems similar to the "Neo-puff" are required that allow pulmonary distension to be encouraged in premature infants from the first insufflations. This equipment achieves its objective by correctly controlling an excess level of pressure in the airway. For this purpose, old Sechrist respirators that are still available in the unit can be used.

2. Human resources:

   The Unit has a staff of experienced personnel who deliver the different modes of mechanical ventilation proposed. Medical staff members taking decisions on a daily basis about ventilotherapy have played an active role in creating this guide, which guarantees they are aware of its existence and their involvement in this. In our circumstances, it is recommended that an internal publication plan be drawn up, aimed at the resident doctors in transit through the unit, and also nursing staff, so that they will understand the cause of their monitoring and surveillance functions.

It is not expected that the use of this guide will cause any interference with the routine clinical care in other neonatal units or with the rest of the hospital. It does not involve the introduction of anything new, but the improvement of something that is already functioning normally. All its effects will be positive.

The group that has prepared the guide wants it to be widely publicised not only internally so that everyone involved should know about it, with particular emphasis on the resident doctors in training, but also for anybody who is interested on it.

Furthermore, the team is aware that establishing well-founded recommendations with the best available scientific information applicable in a specific clinical scenario is not enough. It is also necessary to make additional efforts in order to guarantee that these recommendations are actually incorporated into routine clinical practice, and that they are regularly updated. For the same reason, this guide will be revised within three years, and indicators have been formulated to facilitate evaluation tasks, both for its implementation and the objectives of the guide.

Indicators have been proposed that reflect the practices used in newborn babies on mechanical ventilation and which record their medical history in a systematic manner. They intend to monitor and evaluate the mechanical ventilation provided, any possible changes throughout time and their impact on the clinical results. The following list, which is in no way complete, only includes those who have been of interest, most of which can be obtained in digital form from our hospital's computerised medical records. This digital format consists of a specific record for the neonatology patient that our unit designed in collaboration with the Computer and Documentation Service.

TABLE OF INDICATORS	
Hours of MV* patient-year.	Total hours of MV per year/Total patients undergoing MV per year.
CPAP resuscitation in < 29 weeks in delivery room.	Newborns < 29 weeks resuscitated with CPAP/Total < 29 weeks.
Patients ventilated with a volume-controlled mode.	Patients ventilated with any volume-controlled mode/total patients on MV.
Extubation with nasal CPAP at < 1,500 g.	Patients extubated with nasal CPAP/Total patients undergoing MV < 1,500 g.
HFV at < of 34 weeks.	Patients < 34 weeks on a regime of HFV/Total patient < 34 weeks undergoing MV.

Use of HFV	Total hours of HFV/Total hours of mechanical ventilation.
Prevalence of CPD < 1,500 g.	Patients < 1,500 g fulfilling CPD criteria†/Total patients< 1,500 g.
Frequency of air leaks.	Patients presenting some kind of air leak while on MV/Total patients on MV.
Volume-guided ventilation.	No. of MV sheets** containing the Tv and volume/minute data/Total of sheets for each patient.
Rescue for HFV.	Appearance on MV sheet of the OI prior to starting HFV/Total patients on HFV.

* MV: Mechanical ventilation

** Each patient being put on MV has a record sheet for each day in this situation, which is included on the vital signs record in the NICU.

† According to internationally accepted criteria[116].

ANNEX I

DECISION-MAKING DIAGRAM FOR MECHANICAL VENTILATION

STARTING PHASE

Delivery room | Other setting

In which situations should MV not be initiated?

In which situations should MV be initiated?

How to assess the need for MV?

< 34 weeks GA | Any GA

Systematic intubation at < 29 w?
CPAP support for all?

High frequency or conventional ventilation?

MAINTENANCE STAGE

< 34 weeks | ≥ 34 weeks GA

Pressure or volume controlled ventilation?

Synchronised or un-synchronised MV?

Is sedation necessary with or without paralysis for patients on CMV or HFV?

Which is the best strategy for patient-machine synchronisation?

In severe respiratory failure, conventional or HF ventilation?

Which criteria to use for respiratory rescue with HFV?

WEANING PHASE

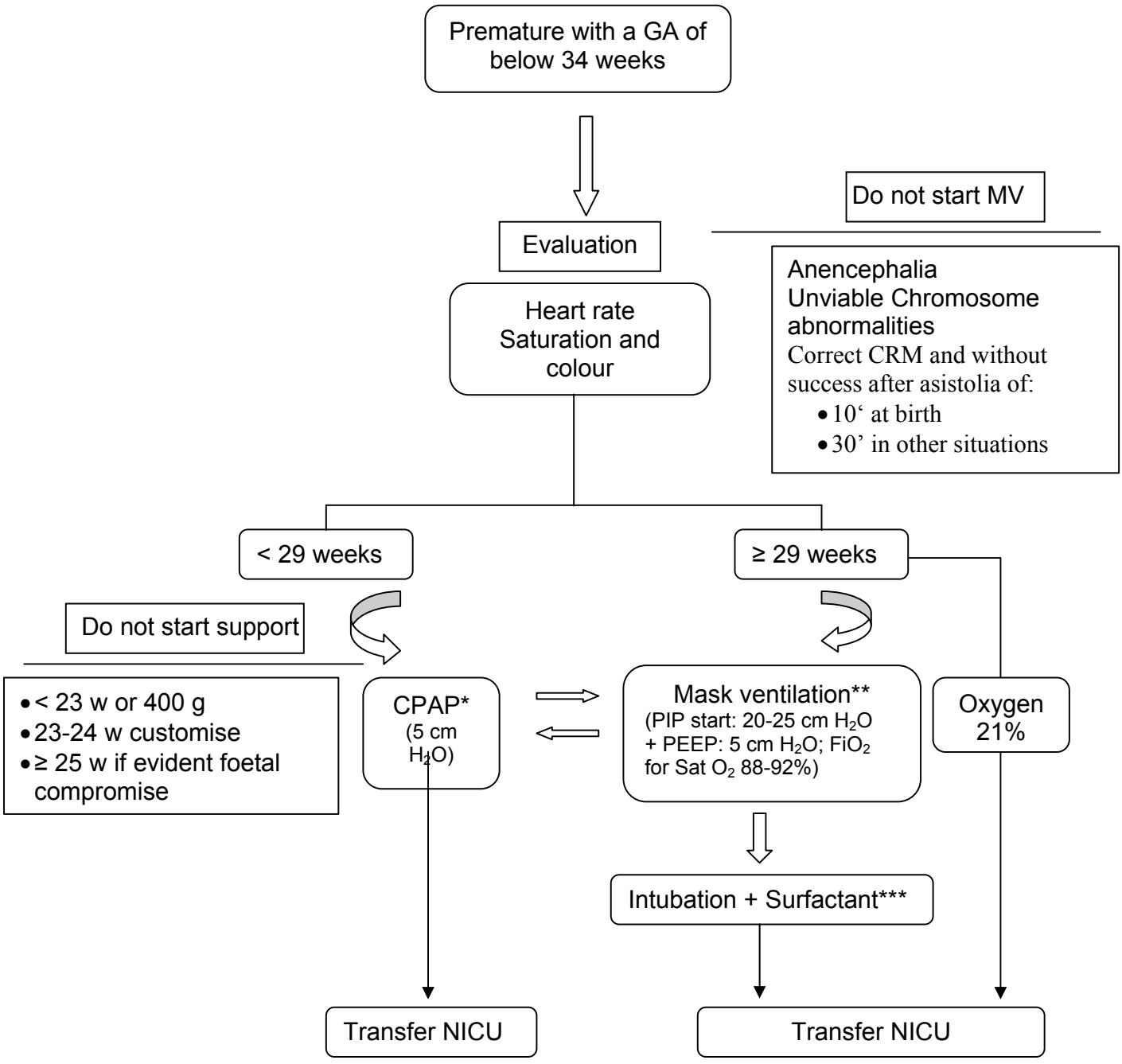
Which is more efficient, direct extubation or an intermediate supporting step with nasal CPAP?

Does the "modus operandi" at the time of extubation depend on the GA and/or body weight?

Is direct extubation safe, without a period of CVM, from HFV?

ANNEX II

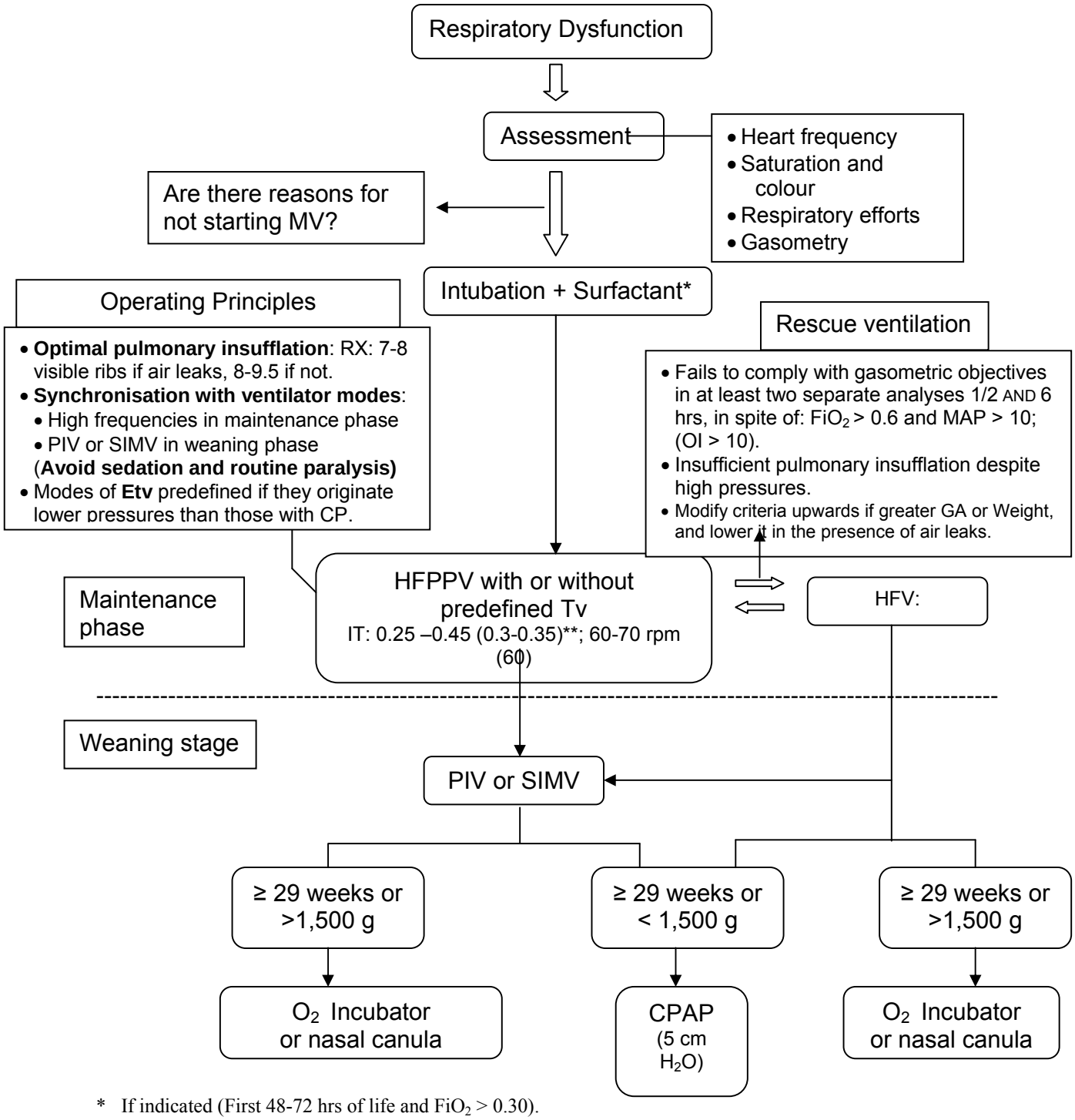
RESPIRATORY SUPPORT OF THE PREMATURE INFANT IN THE DELIVERY ROOM



* Minimal support will be given in all cases, even in the absence of respiratory distress.
** This will apply whenever mask ventilation is required.
*** Intubation will only be carried out based on clinical criteria and the surfactant will be administered on arrival in the NICU.
MV: Mechanical ventilation.

ANNEX III

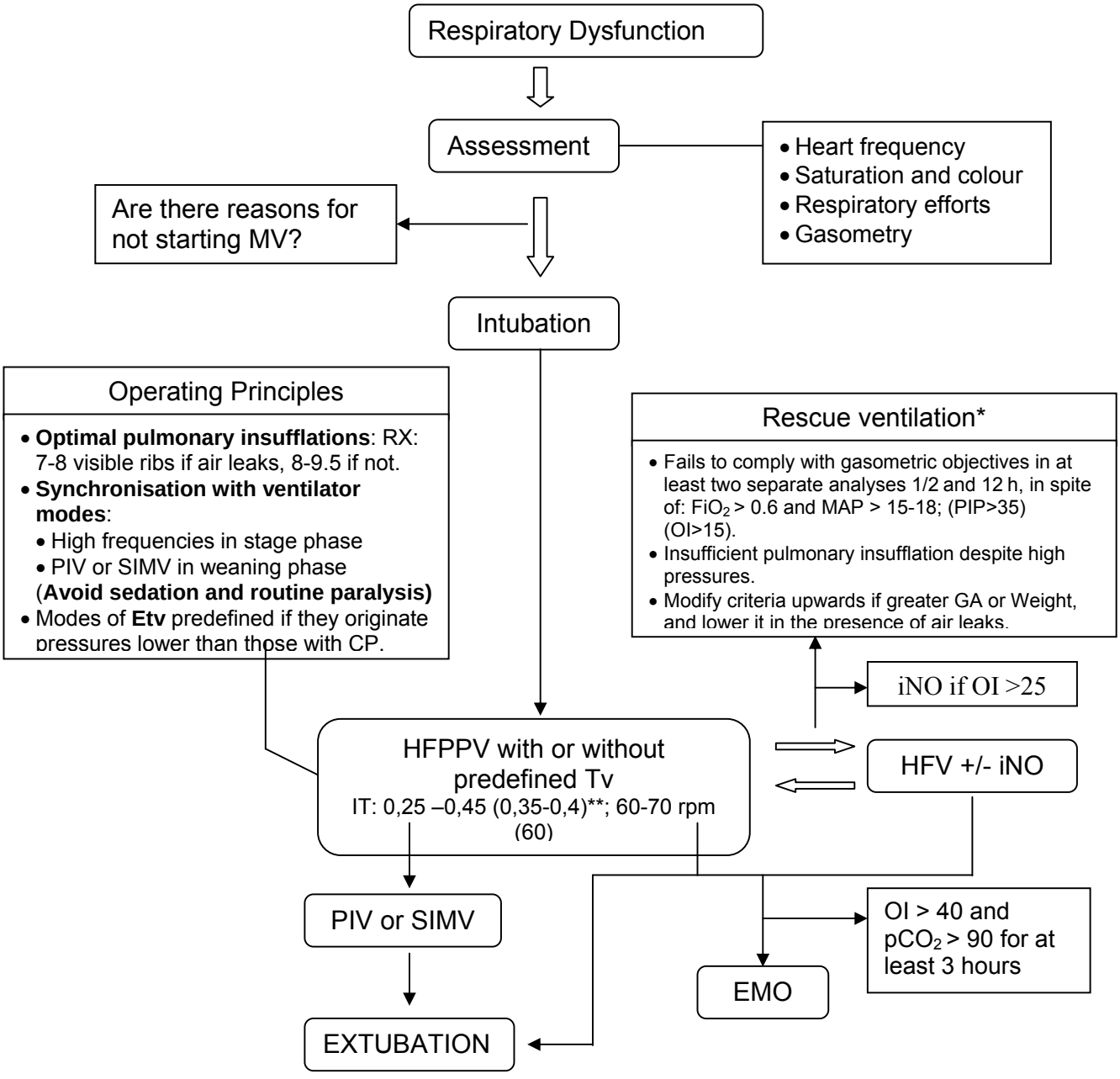
RESPIRATORY SUPPORT FOR PREMATURE INFANTS BELOW 34 WEEKS



* If indicated (First 48-72 hrs of life and $FiO_2 > 0.30$).
** Value suggested in the beginning, and, between brackets, optimum value.
MV: Mechanical ventilation.
IO: Oxygenation Rate.

ANNEX IV

RESPIRATORY SUPPORT IN THE TERM OR NEAR-TERM NEWBORN INFANT



* Assess heart ultrasound scan evaluation.
** Value suggested in the beginning and, between brackets, optimum value.
MV: Mechanical Ventilation.
IO: Oxygenation Rate.

ANNEX V

D GASOMETRIC OBJECTIVES OF MECHANICAL VENTILATION

Normocapnia

Arterial blood

$PaCO_2$ between 35 and 50 mmHg

Permissive Hypercapnia*

Arterial blood

$PaCO_2$ between 50 and 65 mmHg

* Consider as from the 2nd day of MV.

Normoxemia

Arterial blood

Premature:

$PaCO_2$ between 50 and 60 mmHg

pH between 7.25 and 7.45

Term:

$PaCO_2$ between 50 and 60 mmHg

pH between 7.25 and 7.45

- Monitor Saturation O_2
  Ideal values 88-92 (**85-95**)**
- Severe hypoxemia: 40-50 mmHg
- Critical hypoxemia: < 40 mmHg

**** Set alarm limits** ☑

ANNEX VI

☑ **CHANGES TO "CMV "PARAMETERS**

Oxygenation

- The objective that must be achieved is adequate oxygenation with $FiO_2 \leq 0.60$, maintaining optimal pulmonary insufflation according to repeated RX evaluation.
- Depends on **pulmonary insufflation** and **FiO_2**.
- Pulmonary insufflation is controlled by:
  - MAP which is the product of PIP AND PEEP.
  - Increase PEEP before PIP if pulmonary insufflation is not good.
- Prioritise lowering pressure if air leaks exist.

Ventilation (blower)

- The objective is to achieve correct ventilation, assessed by measuring pCO_2, using the lowest **Tv** possible.
- Depends on the **volume / minute** , which is the product of the Tv and respiratoryfrequency. It also includes **pulmonary insufflations** (prevents atelectasias).
- Prioritising high respiratory frequencies over Tv.
- Considering modes with predefined Tve modes if lower pressures are achieved than in CP mode.

Remember:

- Do not make very important changes and **always after clinical control.**
- Carry out clinical control and/or gasometry 30-60 minutes after the changes.

ANNEX VII

☑ **CHANGES TO "HFV" PARAMETERS**

Oxygenation

- The objective that must be achieved is adequate oxygenation with $FiO_2 \leq 0.60$, maintaining optimal pulmonary insufflation according to repeated RX evaluation.
- Depends on the **pulmonary insufflation** – "alveolar recruitment" – and the **FiO_2**.
- Pulmonary insufflation is controlled by **MAP**. Start with +2 cm H_2O over the previous CMV and, if there are air leaks, with the same figure.
- No critical MAP threshold is known which can not be surpassed. It is important to avoid **pulmonary overdistension** – flattening of the diaphragm and/or > 9.5 visible ribs -, which do not lead to better gaseous exchange and also triggers hemodynamic involvement.
- Achieve alveolar recruitment with increases of 1-2 cm H_2O until satisfactory oxygenation is achieved or overdistension starts.
- Prioritise low pressures if air leaks exist.

Ventilation (blower)

- The objective is to achieve correct ventilation, assessed by measuring pCO_2, using the highest frequency oscillations possible.
- It depends on the amplitude of the vibrations, which determine the Tv and the frequency. Optimum **pulmonary insufflation** is also important (avoid atelectasias).
- The correct amplitude is controlled with the visible vibrations to the line of the navel in the Sensor Medic 300A. The Babylog also measures Tv, which must be 1.5-2 ml/Kg, and the DCO_2 (TV^2 x Hz).
- The initial frequency will depend on body weight (for guidance purposes, 15 Hz for premature infants and 10 for term infants). Modify downwards if there is no improvement with maximum amplitude.

ANNEX VIII

☑ **CRITERIA FOR EXTUBATION**

Premature infants with RDS

From CMV:

- Clinical and respiratory stability during at least 6-12 hours with PIV or SIMV support.
- PIV no more than 5 cm H_2O and FiO_2 no greater than 0.25.

From HFV:

- Clinical and respiratory stability during 6-12 hours.
- PIV no more than 7 cm H_2O and FiO_2 no greater than 0.25.

ANNEX IX

SEDATION AND PARALYSIS DURING MECHANICAL VENTILATION

A, B Newborns given mechanical ventilation are neither paralysed nor sedated systematically.

☑ The HFV mode does not necessarily require sedation and neuromuscular paralysis.

☑ If sedation and paralysis are judged necessary, they will be done **individually.** If paralysis is indicated, it must be as brief as possible and after sedation.

Remember → Before administering a drug... ☑

- Make **a full clinical assessment** in order to identify:
  - Ventilation problems: poor positioning and/or obstruction of the endotracheal tube.
  - Mechanical problems with the machine.
  - Changes in the need for respiratory support, due to deterioration in the underlying pneumological process, the appearance of air leaks, complicating pneumonia or other general problems.
  - Need to adjust the ventilation parameters with a view to achieving good patient-machine synchronisation.
  - If the use of neuromuscular blockers are being considered, all of the above must be carried out, and the need to sedate must be considered.
- **Don't forget** to assess the immediate clinical effects of the drug, and particularly their effects on the gaseous exchange.

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Guide

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