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European Consensus Guidelines on the Management of Respiratory Distress Syndrome – 2025

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Abstract
Every year new evidence emerges about how best to care for tiny babies with respiratory distress. We report the seventh version of "European Guidelines for the Management of RDS" by a panel of European neonatologists and an expert perinatal obstetrician based on available literature up to mid-2025. Optimising outcome involves close collaboration with obstetricians to predict risk of preterm delivery, consideration of transfer to perinatal centres and perinatal optimisation including antenatal steroids. Delivery room protocols should include maintenance of normal body temperature whilst aiming to promote spontaneous breathing before clamping the umbilical cord, using non-invasive respiratory support where possible and considering early use of surfactant delivered by thin catheter in an attempt to avoid intubation. Ongoing non-invasive respiratory support and judicious use of surfactant using techniques that avoid intubation will help improve outcomes. If mechanical ventilation is needed, lung protective strategies should be employed and ventilation continued for the shortest time possible to reduce risk of bronchopulmonary dysplasia. Protocols for general supportive care are also reviewed, with an emphasis on good nutritional care, cardiovascular support and judicious use of antibiotics.

These updated Guidelines contain evidence from recent Cochrane reviews and medical literature since 2022. Strength of evidence supporting recommendations has been evaluated using the GRADE system. There are changes to some of the previous recommendations as well as some changes to the strength of evidence supporting recommendations that have not changed.

This guideline has been endorsed by the European Society for Paediatric Research (ESPR) and the Union of European Neonatal and Perinatal Societies (UENPS).

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CI – Confidence interval CLD – chronic lung disease CPAP – continuous positive airway pressure CS – Caesarean Section
DCC – Delayed cord clamping ETT – Endotracheal Tube
ECG - Electrocardiogram FiO_2 – Fraction of inspired oxygen
GA – Gestational age HFOV – high frequency oscillation ventilation
HFOV-VG – HFOV with volume guarantee HFNC – High flow nasal cannula
HR – Heart Rate IMV – Intermittent mandatory ventilation
INSURE – Intubate-surfactant-extubate iNO – Inhaled nitric oxide
IPPV – Intermittent positive pressure ventilation IVH – Intraventricular haemorrhage
kPa – Kilopascal LISA – Less invasive surfactant administration
LUS – Lung ultrasound MAP – Mean airway pressure
MV – Mechanical ventilation NAVA – Neurally adjusted ventilator assistance
NEC – Necrotising enterocolitis NICU – neonatal intensive care unit
NIPPV – Nasal intermittent positive pressure ventilation NIV – Non-invasive ventilation
NIV-NAVA – Non-invasive neurally adjusted ventilator assistance
NNT – number needed to treat NRS – Non-invasive respiratory support
PBCC – Physiological based cord clamping PDA – Patent ductus arteriosus
PEEP – Positive end-expiratory pressure PIP – Peak inspiratory pressure
POCUS – Point of care ultrasound PVL – Periventricular leukomalacia PPV – Positive Pressure Ventilation RCT – Randomised Controlled Trial
RDS – Respiratory distress syndrome ROP – Retinopathy of prematurity
RR – Relative risk SpO_2 – Oxygen saturation
SALSA – Supraglottic Airway Laryngeal Surfactant Administration

VTV – Volume targeted ventilation

Introduction

Optimising outcomes for preterm infants is a priority for those providing neonatal care. Active care for infants as low as 22-23 weeks' gestational age (GA) is increasing although outcomes for this population are variable depending on the region where they are born, and the enthusiasm of the responsible physician for active care in this high-risk population [1]. For infants 24 weeks' GA and above there is a shift towards less invasive management with protocols for management of respiratory distress syndrome (RDS) centred around protecting the delicate lungs from injury. Data on nearly 60,000 babies born at < 1500g from the Vermont Oxford Network and admitted to NICUs show that in 2024 around 75% of 24-26 weeks' gestation babies survive, although rates of bronchopulmonary dysplasia (BPD) remain stubbornly high at 60%. In 2024 nearly 90% of 24–26-week infants received surfactant, dropping to 65% at 27-29 weeks and 32% for 30-32 weeks' GA. Nearly 90% of 24–26-week infants were mechanically ventilated, dropping to 55% at 27-29 weeks and 25% at 30-32 weeks GA (Data available on Nightingale). There is now good evidence that a gentler approach aimed at minimising exposure to the harmful effects of positive pressure ventilation may result in greater numbers of survivors without BPD, but clearly there is more work to be done in terms of convincing clinicians to change practice.

The "European Consensus Guidelines on the management of RDS" were first published in 2007 [2], primarily intended for use in Europe, but with evidence-based recommendations that could potentially be used anywhere, provided that clinicians had access to the resources needed to deliver modern neonatal intensive care. The Guidelines have been updated every three years since 2010 with previous versions collectively being cited over 4400 times, and this being the 7th version, using data from clinical research studies to 2025. RDS is a disorder of surfactant deficiency resulting in clinical signs of respiratory distress from soon after birth that may impact the ability to transition smoothly from intrauterine to extrauterine life. Defining RDS is challenging, with classical definitions such as "ground glass and air bronchograms" on X-Ray being late signs which can be avoided by early non-invasive respiratory support and surfactant replacement therapy. Clinical judgement on work of breathing and oxygen requirements in the delivery room is subjective, but often the only way to decide if surfactant is needed, and babies will be coded as having RDS if they have received surfactant. Therefore, it is difficult to be certain how many infants who receive surfactant genuinely have RDS. The aim of management of RDS is to maximise the numbers of infants who survive without lung injury. Given that manual lung inflations or mechanical ventilation have the potential to cause lung injury there is a delicate balance to be struck. Thankfully many of the interventions employed are studied in randomised trials and many of these are also subjected to systematic reviews. These Guidelines update the previous six versions after critical examination of the most recent evidence up to autumn 2025. As before, we have used a format of summarising the issues in the text followed by evidence-based recommendations according to the GRADE system, to reflect the authors' consensus view of both the strength of the evidence supporting each recommendation, and the strength of the recommendation [3]. Quality of evidence and strength of recommendation are summarised in Table 1. Summary of the recommendations is shown in Supplementary Material 1.

Summary of changes

Prenatal management remains largely unchanged, perhaps with more emphasis on confirming preterm labour, to allow more judicious use of antenatal steroids. In the delivery room we suggest physiological based cord clamping rather than time based, with an emphasis on strategies for managing thermal care if equipment is available before the cord is cut. Starting FiO_2 of 0.6 rather than 0.3 at birth should reduce bradycardia and need for chest compressions and adrenaline for infants born < 29 weeks'gestational age albeit with no differences in other outcomes. Surfactant prophylaxis has reappeared for extremely preterm infants in the current era of Less Invasive Surfactant Administration (LISA), with an emphasis on use of videolaryngoscopy for LISA catheter placement or intubation because of greater first pass success for intubations. Nasal ventilation rather than CPAP now seems the most potent mode of non-invasive respiratory support, both after initial stabilisation and when coming off mechanical ventilation, although there is no unified approach as to how best to provide it. For babies who have not received prophylactic surfactant, the treatment thresholds of FiO_2 0.3 are unchanged, but with more emphasis on using ultrasound where possible to diagnose RDS regardless of FiO_2 requirements in babies with signs of respiratory distress.

Prenatal Care

Lack of antenatal care increases risk of death or severe morbidity [4]. General measures to prevent preterm birth include prevention of teenage pregnancies, adequate pregnancy spacing, prevention of unnecessary caesarean sections, early screening for preeclampsia and treatment with low dose aspirin in women at risk, and single embryo transfer when in-vitro fertilisation is used [5].

Preventing preterm birth

In asymptomatic pregnant women at risk of spontaneous preterm birth, due to either previous preterm birth or where a shortened cervix by the end of the first half of pregnancy has been identified, use of progesterone is associated with a reduced rate of preterm birth and lowered perinatal mortality [6,7]. The efficacy of progesterone in pregnant women with previous preterm birth, who do not have short cervix has been questioned [7]. In twin pregnancies with short cervix, progesterone may decrease risk of very preterm births [8].

Cervical cerclage may also reduce preterm birth in high-risk singleton pregnancies [7,9]. The present challenge is to identify the high-risk pregnancies early and to aim for effective prevention of preterm birth. The same holds for omega-3 fatty acid supplementation, which may also reduce preterm delivery [10], but likely only in populations with poor nutrition.

Place of delivery

Interventions to improve outcomes and prevent RDS begin before birth. There is often warning of impending preterm delivery and there is a need to consider interventions to prolong gestation or to reduce risk of an adverse outcome by "preparing" the foetus. Cervical length measurement, possibly in combination with a biomarker [11] may determine which women are actually at risk of delivery within 7 days, perhaps allow more judicious use of antenatal treatments. Preterm foetuses with expected delivery before 28-30 weeks' gestation should, where possible, be transported in utero to tertiary centres where appropriate skills are available; best outcomes are achieved for immature infants born in high throughput perinatal centres [12]. In cases of prenatal pre-labour rupture of membranes, antibiotics can delay preterm delivery and reduce neonatal morbidity, although co-amoxiclav (Amoxicillin/Cluvalanic acid 4:1) should be avoided because of its association with increased risk of NEC [13].

Magnesium sulphate

Magnesium sulphate, given to women with imminent preterm delivery before 32 weeks, reduces the incidence of cerebral palsy at 2 years of age by about 30%, although longer-term benefits are less clear [14,15]. A reduction of cerebral palsy may be obtained if Magnesium Sulphate is given as little as 4 hours before delivery, so advanced dilation is not a contraindication to treatment [14]. Overdosing must be avoided given the maternal side-effects such as vasodilatation with hypotension and neuromuscular blockage. Tocolytic drugs can be used in the short-term to delay birth, allow safe transfer to a perinatal centre and allow prenatal corticosteroids time to take effect, although beneficial effects on perinatal outcome are uncertain [16]. Of the tocolytic drugs oxytocin antagonists and Ca-channel blockers are quite safe to both foetus and mother and should be used rather than indomethacin. There is little evidence that delivering preterm infants by Caesarean Section (CS) rather than allowing vaginal delivery improves outcome, although it may help around assembling appropriate team for stabilisation when planned electively [17].

Antenatal Corticosteroids

A single course of antenatal corticosteroids (ANCS) given to mothers with anticipated preterm delivery before 34 weeks' gestation improves survival, reduces risk of RDS, NEC and IVH and does not appear to be associated with any significant maternal or short-term fetal adverse effects [18]. Even with modern neonatal care, ANCS are beneficial. The beneficial effects are also evident in low-resource countries when the indications are defined [19]. ANCS therapy is recommended in all pregnancies with threatened preterm birth before 34 weeks' gestation where active care of the newborn is anticipated. Although RCT data is limited in babies at < 25 weeks' gestation, observational studies support the concept that ANCS, together with other active management practices, reduce mortality even down to 22 weeks [20, 21]. The decision to administer ANCS should be concordant with neonatal treatment plans and informing the mother or parents of their desire for either intensive care or palliative care after birth and decisions should always be taken only after full discussion with mothers and partners of potential benefits and risks. [20, 21]. ANCS are associated with a decrease in the early mortality of infants born at 22 to 25 weeks in US academic centres. Death or

neurodevelopmental impairment (NDI) at 18-22 months was lower for the ANCS-exposed infants born at 23-25 weeks [22].

In pregnancies between 34 and 37-weeks' gestation, ANCS reduce risk of short-term respiratory morbidity, but not mortality, and there is increased risk of neonatal hypoglycaemia [23]; with increasing gestation the benefits decrease, whereas the incidence of hypoglycaemia increases [24, 25]. In women in spontaneous preterm labour after 34 weeks, the use of ANCS is therefore controversial and not advisable [26, 27]. The situation may be different in CS without labour in between 34 and 37 weeks, where ANCS are possibly indicated.

The optimal treatment to delivery interval is more than 24 hours and less than 7-10 days, for maximizing the beneficial effects. Beyond 7-10 days benefits are diminished. According to a cohort study, the beneficial effect of the first dose of ANCS starts within the first day, so advanced dilatation should not be a reason not to treat [28]. There is still debate as to whether ANCS should be repeated one to two weeks after the first course for women with threatened very preterm labour. A repeat course reduces the requirement of transient respiratory support; however, it does not further reduce mortality or other serious health outcomes while multiple courses reduces birth weight and head circumference [29]. None of the clinical trials showed any improved outcomes when the repeat course had been given after 32 weeks; a single repeat course should therefore be restricted to a gestational age < 32 weeks [30]. Data on ANCS in multiple gestations are scarce but suggest that they also reduce morbidity and mortality in very preterm birth.

Steroids are potent drugs with many unwanted effects. When given appropriately they improve outcome. If not, then side effects, such as dose-dependent impaired foetal length and head circumference, impaired placental growth, brain apoptosis and increased infection risk may prevail. Long-term follow-up of children from trials conducted in the 1970s has been reassuring. However, when ANCS were given < 34 weeks and delivery takes place at or near term, the neuro-developmental outcome may be disturbed [31, 32]. Data from sibling pairs in Finland raises concerns that any ANCS has a negative effect on neurological, cognitive and behavioural disorders, especially for infants who are born at term [33]. However, the outcomes could have been influenced by the occurrence of preterm contractions, which, in themselves may be a risk factor for neurodevelopmental impairment [34].

ANCS should only be given to women who are highly likely to deliver preterm. This continues to be a challenge, since 40-50% of women receiving ANCS deliver at term with possible adverse outcomes [31, 32]. Unnecessary use of ANCS might be reduced by adequate dating of gestation, preterm birth risk assessment, restriction of repeated courses to a single course before 32 weeks, avoidance of ANCS in women at risk of late preterm delivery and by avoidance of unnecessary early elective CS. The current ANCS dosage appears to be high; betamethasone phosphate results in excessive peak concentrations and the release of betamethasone acetate proceeds slowly for 1-2 weeks [35]. A recent RCT from France compared a single betamethasone phosphate/acetate injection to the regular two injections 24 h apart. The half dosage resulted in a higher risk of need for surfactant treatment within 48 hours: surfactant treatment occurred in 20.0% in the half dosage and in 17.5% of the full dosage-group. There were no between-group differences in the rates of mortality, rates of surfactant therapy, risk of BPD or other important outcomes [36]. Pharmacodynamic studies continue. Maternal BMI and multiple pregnancies might need to be factored in [37]. The same holds for studies in early foetal growth restriction, as ANCS are widely used without focusing on this high-risk group.

Recommendations

1. Mothers at high risk of preterm birth < 28-30 weeks' gestation should be transferred to perinatal centres with experience in management of RDS (**B1**).
2. Ultrasound screening of cervix in high-risk pregnancies and for women with a short cervix in mid-pregnancy, vaginal progesterone treatment in singleton pregnancies to increase gestational age at delivery and to reduce perinatal mortality and morbidity. (**A1**).
3. In women with symptoms of preterm labour, cervical length and accurate biomarker measurements should be considered to prevent unnecessary use of tocolytic drugs and/or antenatal steroids (**B2**).

4. Clinicians should offer a single course of antenatal corticosteroids to all women at high risk of preterm delivery, from when pregnancy is considered potentially viable up to 34 completed weeks' gestation, ideally at least 24 hours before birth (**A1).**
5. A single repeat course of steroids may be given in threatened preterm birth before 32 weeks' gestation if the first course was administered at least 1-2 weeks earlier (**A2**).
6. $MgSO_4$ should be administered to women with imminent delivery before 32 weeks' gestation (**A1**)
7. Clinicians should consider short-term use of oxytocin antagonists or Ca-channel blockers for tocolysis in very preterm pregnancies to allow completion of a course of prenatal corticosteroids and/or in utero transfer to a perinatal centre (**B1).**

Delivery Room Stabilisation

In the delivery room, timings begin when the foetus is fully expelled from the mother, rather than from when the cord is cut. Those attending birth should know how to identify sick infants who require urgent airway management and lung inflation to establish gas exchange and restore cardiac output. *Resuscitation versus Stabilisation*

European Resuscitation Guidelines [38] focus on strategies for how to intervene when infants are born in poor condition secondary to hypoxia, with emphasis on airway opening and lung inflation. However, most babies at risk of RDS will try to breathe on their own. Experimental and clinical studies show that laryngeal closure during apnoea and in between breathing can impede attempts to inflate lungs artificially in infants [39]. It is therefore important to focus on gentle approaches that encourage spontaneous breathing and support normal transition.

Timing of umbilical cord clamping

Not clamping the umbilical cord before the lungs are aerated is an important first step. Avoiding immediate clamping of the cord reduces in-hospital mortality and the combined outcome of death or disability by two years of age [40]. The duration of deferred cord clamping may also be important, with longer deferrals > 2 minutes being associated with the lowest risk of mortality [41]. Physiological based cord clamping (PBCC) describes a strategy of only clamping the cord when the infant has achieved respiratory stability rather than a time-based approach. Specially adapted heated trolleys can facilitate full stabilisation with intact cord close to the mother before the placenta is delivered. Alternatively, delivering the placenta and holding it above baby during stabilisation with the cord intact also shows improved cerebral and peripheral oxygenation, although there are no large trials of this method [42]. The largest trial of PBCC versus time-based clamping using a specialised trolley showed that there was less need for subsequent top up transfusions, less late-onset sepsis, and parents were more content and less anxious when PBCC was performed. Although no overall differences in rates of intact survival were found, there was a significant increase in intact survival in centres with the most use, suggesting a learning curve with the new technique [43]. In a time-based clamping study, where preterm infants were supported by deliberately providing CPAP or manual breaths before the cord was clamped at 120 seconds, rather than just waiting for 60 seconds and then starting stabilisation, did not appear to result in improved outcomes [44]. Umbilical cord milking is an alternative to delayed cord clamping which results in extra blood volume, however with concerns about increased intraventricular haemorrhage for infants less than 28 week's gestation [45]. Recent clinical trials suggest that it is a safe alternative for infants 28 - 32 weeks and could be used in infants born depressed, for whom deferred cord clamping is not feasible [46].

Stimulation

Repetitive tactile stimulation is a well-established method for promoting spontaneous breathing and appears to show some benefit in reducing the need for intubation in an observational study [47], however further randomised trials are underway to determine if it really works (NCT05942924). Very early caffeine increases tidal and minute volumes [48], but it is not known whether efforts to secure IV access for Caffeine immediately at birth will result in any meaningful difference to outcomes. Delivery room enteral caffeine may be a solution; however further dosing and safety studies are needed before recommendations can be made [49].

Early respiratory support

For preterm babies who are breathing, CPAP is considered the best early respiratory support resulting in less lung injury and bronchopulmonary dysplasia (BPD) than intubation [50]. Heated humidified high flow oxygen

has also been used in more mature preterm infants in some centres, but switching to manual ventilation if needed is more challenging [51]. The use of PEEP during resuscitation reduces mortality in preterm babies [52]. T-Pieces are better than self-inflating bags for delivering controlled PEEP levels and consistent tidal volumes if ventilation is needed [53]. If lung inflation is needed, a peak pressure of 25 rather than 20 cm/H_2O is most likely to achieve the desired tidal volume [38]. Peak pressure may require adjustment depending on the infant's response, as recognised by HR increase and SpO2 trajectory. Face mask application, but also binasal prongs may induce apneoa due to stimulation of the trigeminocardiac reflex [54]. A recent randomised trial suggests that nasal interfaces in the delivery room reduced the risk of PPV compared to face masks but made no difference to the need for intubation [55]. Respiratory function monitoring in the delivery room will improve ventilation parameters but at present not widely available and there is uncertainty that it improves outcomes [56]. Choosing a delivery room CPAP system that can be secured easily to the infant's head without the need to hold it in place will allow time (after stabilisation) for delivery room skin-to-skin [57, 58] and surfactant administration if indicated. Good manual ventilation practice, including ensuring that head position is neutral, avoidance of mask leak and airway obstruction, will decrease the proportion of infants requiring intubation [59]. A suggested starting CPAP level of 6cm/ H_2O allows for the CPAP to be titrated either upwards or downwards if needed. Individualised dynamic PEEP strategies are being explored as an alternative to a set CPAP level for very preterm babies to prevent lung injury [POLAR TRIAL NCT04372953].

Thermal care

The World Health Organization (WHO) recommends that the temperature of newborn infants is maintained between 36.5-37.5°C after birth. Delivery room gases should be heated and humidified, and preterm babies ≤ 32 weeks should be stabilised inside plastic bags under pre-heated radiant warmers *in warm delivery rooms (≥ 23°C)* to maintain a normal body temperature [60]. A hat should be placed immediately after birth, however it makes no difference whether the bag is placed before or after the cord is clamped [61].

Early oxygen supplementation

Air oxygen blenders are necessary to allow titration of oxygen during stabilisation. For term babies starting with air (21% oxygen) is best. Preterm babies achieve optimal saturations more quickly if higher concentrations of oxygen are used [62], although there is a balance to be considered around avoiding oxygen toxicity. Although no clear differences in major outcomes are demonstrated whether higher (>0.6) vs. lower (< 0.3) FiO_2 is initiated at birth [63], data from recent clinical trials suggest less need for chest compressions and adrenaline if starting higher (0.6 vs 0.3) in < 29 weeks' gestation [64]. A recent updated systematic review using individual patient data from 1055 babies < 32 weeks in randomised trials also suggests starting at FiO_2 0.9 may be better than <0.3, but data are less clear about the difference between FiO_2 0.9 and 0.5-0.65 [65]. Oxygen levels should be titrated to achieve normal transitional saturations measured by pulse oximetry at the right hand aiming to achieve > 80-85% within 5 minutes [66] as this is associated with better outcomes at 2 years [67]. It is important to be aware that there is a significant time lag between changes in FiO_2 being made at the blender and these equilibrating within the mask, particularly with larger mask sizes in babies requiring small tidal volumes [68].

Monitoring wellbeing during transition

Monitoring of infants during transition consists of assessment of adequate heart rate (HR) and oxygen saturations (SpO_2) that are improving in line with normal values, increasing from 60% to 90% over the first 10 minutes after birth. It may take up to a minute to have reliable pulse oximetry readings for HR and SpO_2, or even longer in extremely preterm babies with low perfusion index. Heart rate can be measured by auscultation, and although ECG is more accurate, it is uncertain whether routine addition of ECG in delivery room confers clinical benefit. Caregivers are usually capable of determining when HR < 60 or above 100 bpm which is all that is required.

Early surfactant therapy and intubation

Once the infant is stable on CPAP, with saturations > 90% and heart rate 120-140, for extremely preterm infants consider an early (selective prophylaxis) dose of surfactant by thin catheter if there are early signs of RDS such as chest retractions, to reduce the risk of needing mechanical ventilation (See later). Some infants remain apnoeic and bradycardic and require intubation for stabilisation, although the number needing intubation can be reduced through quality improvement initiatives focused on delivering effective non-invasive respiratory support [69]. Most extremely preterm infants 22-23 weeks will need intubation for

effective stabilisation and these, or other urgent intubations can be done without sedation. Intubation experience is diminishing, although success rates can be improved through regular simulation training and the use of videolaryngoscopy [70, 71]. If intubation is required then confirmation that the tube is correctly placed should be done clinically, by auscultation as well as using a colorimetric CO_2 detection device if available [72]. Surfactant can be administered prior to radiographic confirmation of tube position, and the infant should be ventilated using a lung protection strategy (see later)

Recommendations

1. If clinical condition allows, defer clamping the umbilical cord for 60 seconds or longer (A1). If stabilisation with intact cord (physiological based cord clamping) can be safely undertaken, longer deferred cord clamping is preferable, especially in infants <34 weeks (**A1**). If DCC is not feasible, consider umbilical cord milking in infants with GA ≥ 28 weeks (**B2**)
2. T-piece devices should be used rather than self-inflating or flow-inflating bag and mask (**B1**)
3. Breathing of preterm infants should be stimulated (**C2**) and supported with CPAP (**A1**). If spontaneous breathing does not occur within 30-60 s, start giving ventilation breaths. Expert consensus is to start with CPAP pressure at least 6 cm H2O and peak inspiratory pressures 25 cmH_2O (**D2**)
4. Oxygen for resuscitation should be controlled using a blender. Use starting FiO_2 of 0.6 for infants <29 weeks', ≥ 0.30 for babies 29 to 31 weeks', 0.21 for 32 weeks' gestation and above. FiO_2 adjustments up or down should be guided by pulse oximetry (**B2**). SpO2 of 80% or more (and heart rate > 100/min) should be achieved within 5 minutes for babies < 32 weeks (**C2**).
5. Intubation should be reserved for babies not responding to positive pressure ventilation via face mask or nasal prongs (**A1**). Use videolaryngoscope and colorimetric capnography if available (**B1**).
6. Room temperature (≥23 °C), plastic bags or occlusive wrapping under radiant warmers and humidified gas should be used during stabilisation for babies < 32 weeks' gestation to reduce the risk of hypothermia. Take additional measures during delayed cord clamping to ensure thermal stability (e.g., thermal mattress). Hyperthermia should also be avoided (**A1**).

Surfactant Therapy

Surfactant therapy improves survival and reduces oxygen exposure, minimises ventilator requirements and pneumothorax. Surfactant therefore plays an essential role in the management of RDS. Prior to 2013, the recommendation for *prophylactic* surfactant was based on evidence from trials predating the current early-CPAP era. Since 2013, recommendations advocate for a more targeted use of surfactant, focussing on infants with relevant clinical signs of RDS. The overall aim remains avoiding MV where possible, whilst endeavouring to give surfactant as early as possible in the course of RDS. Intratracheal surfactant administration has the potential for harm, both by way of its administration and for its potent effect on the respiratory physiology of the lungs. However, in tiny infants with very short gestation of 22-23 weeks, active management almost invariably requires intubation and MV at birth. This population is essentially excluded from present trials involving less invasive treatments [73]. Experience and clinical skills are required to manage the infant whilst preparing the baby for acute intubation, surfactant administration, and subsequent ventilation. Clinical skills are needed to manage the baby safely whilst preparing the baby for surfactant, during the procedure, and for the ventilatory management following surfactant administration [74]. Where possible surfactant should be administered by less invasive methods [75]. This mandates early initiation of CPAP to avoid the harmful effects of intubation and mechanical ventilation (MV) during the transitional phase. If MV is required, a volume-targeted/ volume-guarantee mode should be chosen to minimise ventilator induced injury. (see later)

Surfactant Administration Methods

In most of the early clinical trials, surfactant was given as a bolus through an endotracheal tube, distributed by IPPV followed by a period of weaning ventilation. The Intubate-Surfactant-Extubate (IN-SUR-E) technique pioneered less invasive Surfactant administration and proved successful in reducing lung injury [76]. IN-SUR-E involves Surfactant bolus administration via an endotracheal tube (ETT), followed by brief manual ventilation (via a T-piece resuscitator, or with a self-inflating bag) and no or minimal time on MV. However, based on solid evidence from large RCTs and meta-analyses [77 -79], the current accepted best method is to use a thin catheter for surfactant administration. This approach avoids "bagging" completely and allows the

infant to maintain spontaneously breathing on CPAP while surfactant is gradually instilled in small aliquots. This method, known as less invasive surfactant administration (LISA) or minimally invasive surfactant administration (MIST), results in less need for MV and a reduction in the combined outcome of death or BPD as well as a reduction in IVH in head-to-head comparisons with IN-SUR-E, at identical treatment thresholds [77]. The largest study (OPTIMIST-A) randomised 485 babies of 25-28 weeks with blinding of the intervention: LISA surfactant vs. sham procedure at FiO_2 threshold 30%. Although there was no significant difference in the primary outcome of death or BPD, there was a significant reduction in BPD in survivors favouring the treated infants (37% vs. 45%) [79], and less reported respiratory disease at two-year follow up [80]. However, it is unclear if any differences can be attributed solely to the LISA method, as the benefits of earlier compared to later surfactant in RDS were already known, and two thirds of control infants received surfactant. The LISA technique has been widely adopted in many parts of Europe and in large cohort studies there are better clinical outcomes [81, 82]. However, a definitive large trial may still be needed and there are planned studies exploring the benefits of recruiting the lung through an endotracheal tube to improve surfactant distribution (In-REC-LISA NCT05711966) [83].

Opinion is shifting back to considering routine prophylaxis (via thin catheter) for the smallest babies [84]. In experienced hands, LISA prophylaxis can be used for the smallest infants [85] and the benefits of early, prophylactic LISA are currently being assessed in larger clinical trials [86]. Very recently, Katheria et al. reported on the synergistic effect of early CPAP combined with early surfactant (via LISA) and early Caffeine therapy. In the CALI-trial, spontaneously breathing preterm infants (24 – 29+6 weeks GA) with RDS, were treated either with CPAP, caffeine and LISA (intervention), or with CPAP and Caffeine alone (control). Infants in the intervention arm had significantly reduced rates of respiratory failure within the first 72 hours of life (23% in intervention group vs 53% in the control group) [87]. Two-year follow up from two large, randomised trials also give reassurance that the LISA technique is safe [80, 88]. Early rescue with LISA also has potential to reduce oxygen exposure, air leaks, MV and overall costs of care [89]. When training practitioners in thin catheter placement (or intubation) the use of videolaryngoscopy may increase the chance of first attempt success [90].

Laryngoscopy for LISA surfactant is undoubtedly uncomfortable, but there is more risk of apneic episodes post-procedure requiring PPV if sedation is used [91]. In practice, the ease of the procedure seems unaffected whether opiates, oral sucrose or no sedation are used [92]. Further clinical trials are underway to assess benefits and risks of sedation for LISA surfactant [93]. Alternative methods of delivering adequate quantities of surfactant to the lung in a gentler manner would be ideal. Laryngeal masks (LM) can be used to administer surfactant in babies [94, 95], however currently not yet widely adopted as routine management [96]. A recent study confirmed non-inferiority of LM-Surfactant to IN-SUR-E in preterm babies as low as 800g, probably related to sedation protocols for endotracheal tube placement [97]. A large multinational RCT, comparing laryngeal mask surfactant to routine care in over 900 premature infants is currently underway [SURFSUP Trial (ACTRN12620001184965)].

Alternative methods of surfactant administration have been studied, including prophylactic oropharyngeal instillation of surfactant which does not work [98]. Nebulised surfactant remains a contender, especially since modern nebulisers are capable of aerosolising surfactant [99]. However, to date studies on nebulisation have not convincingly shown any meaningful improvement in smaller infants who should benefit most [100, 101].

When to Treat with Surfactant?

All 22- and 23-week gestation infants are considered a special group of patients that are likely to need planned intubation and surfactant in the first minutes after birth before they deteriorate. If intubation is deemed necessary as part of stabilisation for infants between 24- and 30-weeks GA, then surfactant should be given immediately to improve lung compliance and promote early extubation [102]. Most preterm infants will transition successfully on CPAP but those with RDS are likely to develop progressively worsening lung disease, clinically presenting as increased work of breathing, sternal recession and increasing oxygen requirements to maintain normal saturations. Following the natural course of RDS, spontaneous recovery usually begins after 48–72 h, and infants with milder disease may manage without surfactant, thereby avoiding the discomfort of laryngoscopy and potential deleterious effects of intubation. The dilemma for modern day neonatologists is when to intervene with surfactant. Surfactant deficiency is most severe at birth in infants developing RDS and endogenous surfactant production increases gradually during the first 3-

5 days after birth. Providing exogenous surfactant in surfactant deficiency before the lung injury and deficient gas exchange develops is beneficial. The efficacy decreases in full-blown RDS, involving alveolar - airway injury and dysmorphic airspaces loaded with surfactant inhibitors and inactivated surfactant. At present RDS severity is determined clinically, using a combination of FiO_2 requirements, coupled with judgement of work of breathing and other signs of respiratory distress alongside the degree of lung aeration on chest radiograph (or ultrasound), all of which can be influenced by CPAP [103 - 105]. Ideally, predicting surfactant deficiency before the infant has deteriorated would enable earlier surfactant therapy in infants on CPAP and is likely to result in less need for MV and improved outcomes. Our previous recommendation to use $FiO_2 \geq 0.30$ as the threshold for surfactant treatment was based on observations of CPAP failure rates according to early postnatal oxygen requirements and is supported by more recent data [106, 107]. In these studies, FiO_2 at two hours of life was used to predict later CPAP failure, which was defined as oxygen requirement of 50-60% or more. In a more recent similar study, CPAP-failure was defined as oxygen requirement of 30% and thus optimal prediction was obtained at a 2-hour FiO_2 as low as 23% [108]. As RDS is typically progressive over the first days of life, it is no surprise that FiO_2 cut-off for surfactant administration should be age specific. Furthermore, the use of early nasal ventilation and the knowledge that simply increasing mean airway pressure is likely to lower FiO_2 requirements, even in surfactant-deficient infants, contributes to the debate of optimal FiO_2 cut-off [109]. Evidence is consolidating that lung ultrasound, with appropriate training, is a reliable technique for diagnosing RDS within 2 hours of age [110], without resulting in more infants overall being treated [111]. Evidence on reliability of LUS assessed in RCTs including over 700 infants was reviewed by Capasso and co-workers [112]. According to their results, the sensitivity of LUS for detecting poor aeration and surfactant need was 0.86, thereby superior over adjudging surfactant need by FiO_2 (30%) only. Whilst LUS is increasingly being practiced, debate continues about which LUS scoring system be considered the gold standard [113]. Rapid bedside testing for surfactant components in gastric aspirate (L/S ratio) has been extensively studied, usually allowing a decision on surfactant need to be made within 90 minutes where laboratories are capable of processing gastric aspirate samples. However a recent clinical trial of bedside test kit has shown disappointing results [114]. Lavizzari and Veneroni reviewed the accuracy of postnatal biochemical and lung function tests performed within 3 h from birth for predicting surfactant need in preterm infants ≤34 weeks' gestation. Analysing data from eight studies, including 810 infants, authors concluded that current evidence is insufficient to recommend biochemical and lung function tests [115]. Further research using lung oscillometry as a predictive test is planned [NCT05791331]. The current evidence for more mature infants with signs of RDS indicates a potentially decreased risk of mortality, air leaks, persistent pulmonary hypertension and duration of respiratory support. However, due to heterogeneity of data, there is currently not enough evidence to make any recommendations [116]. The SURFON trial, which has recently finished, should hopefully help decide whether to treat late preterm and early term infants with early signs of respiratory distress [117].

Repeated Surfactant Dosing

Occasionally, more than one dose of surfactant is needed. The need for more than one dose of surfactant is assessed clinically, based on persistent X-Ray changes, work of breathing, ventilation settings and oxygen requirements. Lung ultrasound may be just as helpful in making treatment decisions for repeated doses of surfactant as for the first dose [118]. Many infants can continue on non-invasive respiratory support even when surfactant is required. If poractant-alfa is used, the need for re-dosing can be minimised by using a larger initial dose of 200 mg/kg [119]. For other surfactants such data are not available.

Surfactant Preparations

There are three natural (animal-derived) surfactants currently available in Europe, the bovine derived Beractant and Bovactant and the porcine derived Poractant alfa. Beractant (Survanta®) at recommended dose of 100 mg/kg requires surfactant dose volume of 4 mL/kg. Bovactant (Alveofact®) at recommended dose of 50 mg/kg requires volume of 1.2 mL/kg. Poractant alfa (Curosurf®) at recommended dose of 100-200 mg/kg requires dose volume of 1.25-2.5 mL/kg. The majority of data from recent clinical trials is derived from poractant alfa studies. Head-to-head trials show similar efficacy among surfactants when used in similar doses, however there is a survival advantage when poractant alfa at the higher dose of 200 mg/kg is compared to 100 mg/kg of poractant alfa or beractant [120]. In practical terms delivery suite weight and dose estimating with whole vial use is implemented in many centres, although this strategy is still being

tested in a clinical trial [121]. Fully synthetic surfactant would be ideal, but these are not yet commercially available. Adding budesonide to surfactant does not affect clinical outcomes and should not have a role in early respiratory management [122, 123].

Surfactant use outside of RDS

Although outside the scope of these guidelines, surfactant therapy may be useful in other serious situations where secondary surfactant inactivation occurs such as pulmonary haemorrhage [124], in severe pneumonia [125], or meconium aspiration syndrome. It has no role in evolving BPD and is not recommended in infants with congenital diaphragmatic hernia [126].

Recommendations

1. Surfactant should be given early in the course of the disease, whilst on non-invasive respiratory support (**A1**). Consider selective prophylaxis within the first hour of life for infants < 28 weeks with early signs of RDS after stabilisation (**B2**).
2. If preterm infants < 32 weeks' gestation require intubation for stabilisation, surfactant should be given as soon as possible (**A1**).
3. For infants >28 weeks, surfactant should be given to infants with worsening RDS (**A1**). A suggested protocol would be to give surfactant to infants on non-invasive respiratory support with a mean airway pressure (MAP) of ≥ 6cm H_2O, an FiO_2 of ≥ 0.3, or where lung ultrasound suggests surfactant need (**A1**).
4. Thin-catheter (with videolaryngoscope **(C2))** is the preferred route of surfactant administration for spontaneously breathing preterm babies (**A1**).
5. Supra-glottic airway devices may be used for surfactant delivery for larger infants (**B2**).
6. An initial dose of 200 mg/kg is better than 100 mg/kg of poractant alfa (**A1**).
7. A second and occasionally a third dose of surfactant should be given if there is ongoing evidence of RDS such as persistent high oxygen requirement and other problems have been excluded (**A1**).
8. Surfactant can be used for RDS complicated by congenital pneumonia (**C2**) and can improve oxygenation following pulmonary haemorrhage (**C1**).

Oxygen Supplementation beyond Stabilisation

The Neoprom collaboration confirmed that targeting lower saturations (85-89% vs, 91-95%) could protect against retinopathy of prematurity, but at the expense of increasing mortality (RR 1.17; 95% CI 1.04 - 1.31) and necrotising enterocolitis (1.25 (1.05-1.49)) and the current standard is to recommend targeting saturations in this higher range [127, 128]. It is acknowledged that there is limited data on where to set alarm limits to achieve these goals [129] but setting tighter alarm limits of 89 to 95% may prevent fluctuations and avoid excess hypoxaemia and hyperoxia. Servo-controlled oxygen delivery will help to keep infants in the desired range when on mechanical ventilation or non-invasive respiratory support and may reduce nursing workload, however there is no evidence to date that they improve outcomes [130 - 132].
Taylor and co-workers did a retrospective cohort analysis of preterm infants <29 weeks born between 2011 and 2018 comparing intermediate SpO_2 targets, that is, SpO_2 88–93%, with high targets, 90–95%. Gestational age and birth weight were comparable with the NeOProM studies. Survival without morbidity was higher in the intermediate target group compared to the high SpO_2 target group (aOR 1.59, 95% CI: 1.04–2.45). There was no difference in mortality (aOR 0.81, 95% CI: 0.59–1.11), NEC (aOR 0.90, 95% CI: 0.69–1.18), or severe ROP (aOR 1.26, 95% CI: 0.80–1.97). Further, there were no differences between the two groups regarding severe brain injury. The authors also examined the effects of alarm limits. Alarm limits between 83–95% versus 88–97% were linked to higher survival (aOR 1.67, 95% CI: 1.05–2.65). Although a low SpO_2 target group was not included in this study, these results indicate that an intermediate SpO_2 target leads to similar mortality as in the high group without increasing the risk of severe ROP. The study therefore suggests that a SpO_2 target of 88–93% is preferable to 90–95%. It also indicates that alarm limits should not be higher than 95%.[133] So targeting 85-89 % should be avoided, uncertainty remains whether intermediate targets (88-93) are better than higher targets (90-95). This will need to be addressed in further randomized studies before firm recommendations can be made.

It is also unclear if targeting even higher saturations might improve survival yet further, albeit at the expense of more retinopathy. Shifting the upper limit to 97% causes a right shift in saturation distribution with less time spent < 90% and more time > 97% but no change in time of transcutaneous oxygen exceeding 10.7 kPa and perhaps future studies could assess benefits and risks of targeting wider limits in a relatively safe way [134]. Around 20% of babies with evolving BPD will develop pulmonary hypertension and perhaps for these infants it would be reasonable to increase alarm limits to 97% to enable more time to be spent at the upper limit of the target range of 92 – 95% [135].

Recommendations

1. In preterm babies < 28 weeks GA receiving oxygen the saturation target should be between 90-94% (**B2).** Consider increasing target saturations for babies with BPD and pulmonary hypertension **(B2)**
2. Alarm limits should be set to 89% and 95% (**D2**)
3. Protocols for screening and treating preterm babies for ROP should be in place (**A1**)

Non-Invasive Respiratory Support (NRS)

Use of continuous positive airways pressure (CPAP) as first line mode of respiratory support was pioneered by Jacobsen et al. in the early 1990s' [136]. In 2008, the COIN trial was first large scale randomised trial to provide more robust evidence that babies did not need intubated and ventilated, confirming that they can do just as well if started on CPAP [137], with subsequent large, RCTs confirming that initiation of CPAP, rather than routine intubation for surfactant administration resulted in less lung injury [138].

CPAP

CPAP has been used for more than 50 years and improves lung volume and functional residual capacity, thereby improving oxygenation and reducing the work of breathing and the frequency of apnoeic episodes. CPAP delivers heated and humidified gas, at a set pressure (that can be controlled, typically between 5 and 10 cm/H_2O) through an interface such as nasal mask or prongs that fit tightly to the baby's nose, secured using ties to a hat or straps around the head. There are some advantages of nasal masks over prongs in terms of treatment success [139]. Leaks are common, and nasal injury can occur, but rotation between mask and prong may not be superior to the use of mask alone [140]. Higher pressure improves oxygenation but has the potential to risk air leaks or cause gastric over distension, and clinicians need to make judgements as to how much pressure is needed for an individual infant at any given stage of their RDS journey.

Constant or variable-flow devices can generate CPAP. "Bubble CPAP" simply uses a gas circuit connected to an underwater seal with the theoretical advantage of the bubbling causing small oscillatory pressure fluctuations, which could improve CO_2 washout and lung recruitment. These low fidelity, albeit effective devices are comparatively less expensive and more readily available in lower income settings [141]. CPAP can also be provided through modern mechanical ventilators or variable-flow driver devices. There are no striking advantages with any particular CPAP generating system [142] but being able to change quickly among the various other potentially more efficacious methods of providing non-invasive support needs to be considered. Variations of "classical" nasal CPAP that have been studied include bi-level CPAP, nasal ventilation (both synchronised and unsynchronised) and nasal high frequency oscillation, which employ controlled pressure increases above the baseline CPAP pressure at set frequencies that will potentially enhance the dead space clearance, as well as increase the overall mean airway pressure. In addition, heated humidified high flow nasal cannula (HFNC) can deliver gas at set flows via nasal cannulae specifically designed not to occlude the nostrils. These undoubtedly will create a degree of pharyngeal distending pressure (which is not measured) akin to CPAP but may also work through alternative mechanisms such as nasopharyngeal dead space washout. Finally, NIV-NAVA (non-invasive Neurally Adjusted Ventilatory Assist) in preterm infants offers both advantages of an efficient synchronization with the diaphragm and the provision of pressure assistance proportional to the spontaneous infant's drive. These alternative methods of non-invasive respiratory support have been compared with CPAP, both as a primary mode of respiratory support and as a mode of support when coming off mechanical ventilation with some differences in outcomes starting to emerge. Clinicians can judge the success of each mode based on shorter term outcomes such as perceived comfort or ability to avoid escalation to intubation and ventilation,

which should in turn be reflected by evidence of reduced lung injury, such as reduction in BPD (Oxygen dependency at 36 weeks' gestation).

Nasal ventilation

Bi-Level CPAP devices (BiPAP, DuoPAP) that produce low pressure differences (inspiratory pressure 9-11 cm H_2O only) at rates of around 20-40 with prolonged inspiratory time have not so far shown any meaningful advantages over CPAP alone [143]. When referring to NIPPV we are talking about pressures similar to those delivered when on mechanical ventilation being given through a nasal interface [144]. Modern ventilators can partially compensate for the leaks when ventilating through a non-sealed system (open mouth) but have potential for gas insufflation of the stomach. The frequency and inspiratory time of the ventilations can be set, or they can be triggered by in line sensors that can detect small pressure or flow fluctuations generated by inspiratory effort, or abdominal capsules, or in the case of neurally adjusted ventilator assistance (NAVA) by the diaphragm electrical activity.

The most recent systematic reviews show that when used as a primary mode of respiratory support NIPPV is superior to CPAP in terms of reducing need for intubation (RR 0.67 (0.56–0.81)), and also has the potential to reduce BPD if synchronisation is used (RR 0.52 (0.27–1.00)), with the caveat that the majority of babies studied were between 28 and 32 weeks' gestation and therefore uncertainty about whether this is true for smaller infants and concerns about the heterogeneity of the studies included in these reviews [145 - 147]. Additionally, it has been pointed out that previous trials of NIPPV versus other forms of NRS used a plethora of pressures, i-times and ventilator rate settings, making it difficult to advise on optimal settings when using NIPPV.

High Flow Nasal Cannulae

When comparing HFNC to CPAP as primary mode of support there are more treatment failures with HFNC (RR 1.70 (1.41–2.06)) but because they can be rescued with CPAP there was no overall increase in numbers requiring mechanical ventilation (RR 1.04 (0.82- 1.31)) and significant decrease in nasal injury with HFNC (RR 0.49 (0.36 0.68)) [148]. These studies focused on babies > 28 weeks' gestation and there is uncertainty if they can be extrapolated to smaller babies. HFNC has also been compared to NIPPV in four studies, but numbers remain small. [148]. HFNC can also be used to support infants during intubation to prevent profound hypoxia [149].

Nasal HFOV

Nasal HFOV has also been compared to CPAP, both as a primary mode of respiratory support and for infants post extubation, with studies mostly undertaken in low to middle-income countries [150]. Meta-analysis of these studies which include more than 5000 preterm babies suggests that intubation rates can be reduced if used as primary support (RR 0.52 (0.33–0.82)) and also re-intubations if used post extubation (RR 0.42 (0.35 to 0.51)) with corresponding reductions in BPD (RR 0.78 (0.67 to 0.91)). More recently, a larger multicentre clinical trial from China included 342 infants less than 29 weeks' gestation and showed that nasal HFOV was superior to CPAP in terms of reducing the risk of needing intubated within the first seven days, although no demonstrable reduction in BPD, and the MAP was higher in the HFOV arm. [151]

Support when extubating

NIPPV is superior to CPAP as choice of support for infants coming off mechanical ventilation in terms of need for re-intubation (RR 0.78 (0.70-0.87)) and if synchronised may also reduce air leak and BPD ((RR 0.64 (0.44 to 0.95)) [152] although relatively few babies <28 weeks' are included in studies. HFNC compared to CPAP post extubation results in more treatment failure [153], although rescuing with CPAP means that re-ventilation rates not necessarily increased and for bigger babies may be a reasonable, more comfortable option if CPAP is available as a back-up.

At present it is not clear whether NIPPV works better because of the increased mean airway pressure or if it is an effect of the ventilation per-se. Recently the ECLAT trial showed that extubating preterm babies < 28 weeks to higher CPAP pressures (9-11 vs. 6-8 cm H_2O) resulted in less need for re-ventilation within 7 days [154]. As with nasal HFOV, larger trials with contemporaneously high, and equivalent mean airway pressures settings in all studied groups are needed to compare NIPPV to CPAP [147]. Until such evidence is available,

it may be best to have access to several NRS modes so that the most appropriate can be chosen, and infants can be smoothly moved between NIPPV, CPAP and HFNC, according to gestation and clinical need. However, where resources are limited, it may be better to ensure that all staff can master a selection of these modalities. When weaning babies from CPAP, a gradual reduction in pressure rather than sudden cessation of CPAP results in greater likelihood of success [155]. An extended use of CPAP in infants < 33 weeks' gestation may improve lung growth and function [156] but this approach requires further investigation and may impact on the diagnosis of BPD.

Synchronisation with babies own breathing efforts can be achieved with abdominal capsules, flow triggers and pressure triggers which have not been rigorously compared in clinical trials. NAVA offers the shortest trigger delay and is therefore an attractive option for non-invasive support (NIV-NAVA), but because it is not widely available and relatively expensive NAVA has not been studied as much as other modes. A recent systematic review of five studies shows no advantage over CPAP when used as the primary mode of support, but when used following extubation NAVA reduced need for reintubation compared to CPAP or NIPPV, although more data from larger studies are needed before firm recommendations can be made [157]. The recently commenced DIVA trial [NCT05446272] will hopefully help close this evidence gap [158]

Recommendations

1. Non-invasive respiratory support (NRS) should be started from birth in all babies at risk of RDS who do not need intubation for stabilisation (**A1**).
2. Nasal CPAP at 6-8 cmH_2O or, if available, NIPPV (*preferably synchronised)* should be used as the primary mode of NRS (**A2**). Ability to escalate to NIPPV from CPAP will reduce the need for invasive MV in some infants (**A1**).
3. BIPAP devices confer no advantage over CPAP alone (**A2**).
4. Following extubation synchronised NIPPV can reduce need for re-ventilation and may reduce BPD (**A2**).
5. The interface for providing NIPPV or nCPAP should be short binasal prongs or nasal mask (**A2**).
6. HFNC reduces nasal discomfort and can be used as part of weaning NRS (**A2**)

Mechanical Ventilation Strategies

Maintaining small infants on NIV is not always achievable. For the smallest of infants, born at the margins of viability, it may be safest just to intubate them at birth [159]. Overall preterm infants who are well enough to avoid ventilation do better, [160] but despite best efforts around half of all extremely preterm babies need mechanical ventilation at some stage, even after receiving prophylactic surfactant [81]. It is therefore imperative that those caring for preterm babies with RDS fully understand the principles of mechanical ventilation (MV) to avoid the risk of causing lung injury, and this is one of the arguments for centralisation of care for extremely preterm infants to achieve better outcomes [12]. The aim of MV is to provide acceptable blood gases by using positive pressure, set to levels that aim to achieve tidal volumes in an "open lung" that avoids over-distension, as well as avoiding atelectasis. Over distension of the lung will cause air leaks and pulmonary interstitial emphysema, whilst ventilating at too low a pressure will cause repeated opening and closing of collapsed atelectatic lung leading to injury and inflammation. It is important to use sufficient positive end expiratory pressure (PEEP) to keep the lung open during expiration, as well as avoiding excessive peak inspiratory pressures (PIP). What makes this challenging is that the requirements of an individual infant vary quickly over time: In one instant the pressure needed to open a "stiff" lung may be high, but following treatment with surfactant the compliance improves rapidly, with much lower inspiratory pressure requirements needed to deliver effective tidal volumes and a lower PEEP to maintain an open lung. To overcome this, clinicians should be familiar with methods of ventilation that can protect the lung such as volume targeted ventilation (VTV) or high frequency oscillation ventilation (HFOV). [161]

Synchronisation of ventilation

Modern ventilators have flow sensors that can measure the volume of gas entering and leaving the lung. This enables the ventilator to time MV to coincide with the babies own breathing efforts (synchronisation) as well

as limiting the volume entering the lung with each breath avoiding overdistension. Synchronisation results in less time on MV [162].

Volume targeted ventilation (VTV)

VTV leads to automatic weaning of pressure as compliance improves. VTV compared to pressure-controlled ventilation leads to earlier extubation, fewer air leaks and less BPD [163]. This comes with the caveat that only around 200 babies < 1000g have been included in clinical trials included in the Cochrane Review, and therefore less certainty about the impact on BPD in this population, however VTV can be used even in the smallest babies and reduces the risk of hypocarbia [164]. When using VTV set the initial tidal volume to around 5mL/kg and set a maximal PIP to a safe level of around 25-30 cm H_2O, with a backup respiratory rate of around 30 *(in case of apnoea)*. Be prepared to adjust tidal volumes based on blood gases and perceived work of breathing, but if gases are good and the baby comfortable then leave the settings alone, as the delivered PIP should automatically wean. We lack clinical methods to monitor the functional residual volume. X-ray and ultrasound are helpful, but systematic use in this context has not been investigated. The PEEP can be adjusted to maintain an open lung by finding the pressure at which the FiO_2 is lowest with haemodynamic stability. Respiratory oscillometry and electrical impedance tomography may also assist clinicians in titrating the optimal PEEP during ventilation (as well as the optimal MAP during HFOV) [165]. The required tidal volumes are usually around 5-7 ml/kg, tending to increase with increasing postnatal age or evolving BPD. VTV may not always be possible, particularly if there is a large leak around the endotracheal tube so it is important to understand alternative modes of providing respiratory support.

High Frequency Oscillation Ventilation

HFOV is a lung protective strategy that allows very small tidal volumes to be used at fast rates (typically10-15Hz, and occasionally up to 20 for very small infants) on an optimally inflated lung, held open using a continuous distending pressure. Compared with conventional pressure-controlled ventilation it reduces BPD [166] with the best outcomes being achieved if an "Open Lung" concept is adopted [167]. This involves learning how to determine the optimal distending pressure for an individual infant at a set moment in time, by finding the pressure at which oxygenation deteriorates after stepwise reduction from full lung inflation and setting the pressure 1-2 cm H_2O above this. It is important to be aware that as lung compliance improves, the distending pressure may result in overinflation if the pressure is not weaned [168]. In HFOV the frequency is typically set around 10HZ for more mature infants and faster (12-20 HZ according to size) for smaller babies [167] with amplitude adjusted to observe chest wobble as a starting point. Once the frequency is set then adjustments in amplitude are made to control CO_2 elimination. Frequency adjustments are only needed if amplitude adjustments are unsuccessful, however by decreasing the frequency this leads to larger volume oscillations that in turn can help with CO_2 clearance. Alternatively, HFOV can be used in volume guarantee mode (HFOV-VG]. In this mode the ventilator will automatically adjust amplitude to achieve a desired tidal volume with each tiny beat, and this reduces the risk of hyper or hypocarbia [169] and may also be lung protective [170]. In HFOV-VG, adjustments are made to the tidal volume to control CO_2 elimination and frequency adjustments have the opposite effect of when on conventional HFOV, with decreasing frequency leading to decreasing CO_2 clearance.

Neurally adjusted ventilatory assistance (NAVA)

NAVA can also be used to improve synchronisation when on MV and thereby improve patient comfort and facilitate better oxygenation and CO_2 clearance, even in babies with evolving BPD [171]. A recent systematic review shows that NAVA helps to lower PIP, but with only 200 infants included in randomised trials to date, no differences in BPD rates were found [172]

Whatever ventilation system is used within an individual unit, it is important that all staff should be familiar with it, and that policies are in place to determine which mode to use and when.

Inhaled Nitric Oxide in preterm babies

Inhaled nitric oxide (INO) is a potent pulmonary vasodilator with demonstrable benefits in term infants with pulmonary hypertension. Large clinical trials in preterm infants with hypoxic respiratory failure showed that it conferred no benefit [173] and in cohort studies preterm infants who receive INO therapy have worse outcomes, although this is not likely cause and effect [174]. However preterm infants with demonstrable pulmonary hypertension, particularly those with a history of maternal prelabour preterm rupture of

membranes can respond well to INO therapy [175]. Those who respond have better outcomes [176, 177], and these infants may do just as well as term babies in terms of INO response [178]. Therefore, it is reasonable to recommend assessing hypoxic preterm babies for pulmonary hypertension and treating with INO if it is present.

Extubation

Once stabilized on MV with demonstrable spontaneous breathing effort clinicians should plan when infants can be extubated to NIV. Some babies will only require a very short period of MV, particularly those with RDS for whom surfactant therapy has been successful, and extubating babies who are on low ventilator settings should be encouraged. Factors determining extubation readiness are complex, but include infant's weight, presence or absence of growth restriction, postnatal age, oxygen requirements and blood gases [179]. Mathematical models for predicting extubation readiness have not been successful [180], nor has lung ultrasound [181] and impedance tomography only shows differences once extubation has already occurred [182]. Trials of spontaneous breathing through the ET-Tube on CPAP are also not helpful [183]. Extubation is possible from when MAP reaches about 7-8 cmH_2O on conventional ventilation or a CDP of 8-9 cmH_2O on HFOV. Clinicians need to balance the benefits of getting off the ventilator more quickly versus the risks of repeated intubations with ventilation.

Caffeine Therapy

Caffeine is a well-established aspect of newborn respiratory care [184], with strong evidence that when used for apnoea, or before extubation that they will reduce time on respiratory support and reduce BPD, and thereby improve neurodevelopmental outcome [185, 186]. It seems that the earlier caffeine therapy is initiated, the better the outcome [187]. Recent systematic reviews have again confirmed benefits in apnoea and BPD reduction and well as longer term benefits in motor function [188] with the biggest benefit found when higher doses are used. Higher dosing regimens of caffeine may further reduce BPD [189] but there is limited data on longer term outcomes and side effects and wide variation in practice in terms of loading and maintenance dosing regimens [190]. Higher dose effects are currently under study in the BABYCCINO-Trial [NCT06972849],, which is part of a large Australasian platform study (PLATIPUS NCT06461429). Prophylactic caffeine beginning soon after admission may have the added benefit of reducing time on mechanical ventilation [191, 192] and some study protocols are exploring the use of enteral caffeine in the delivery room [193]. Caffeine is also being explored as a potential neuroprotective drug in late preterm infants in the "Latte Trial" [ANZCTR ACTRN12622001344785] [194].

Permissive Hypercapnia

It is accepted practice that tolerating mild degrees of hypercapnia has the potential benefit of facilitating earlier extubation, however to date there is no strong evidence that this practice results in any meaningful differences in rates of BPD [195] and there is significant uncertainty about which levels are safest, but CO_2 around 5-7 kPa is probably best [196]. Hypocapnia should be avoided because of its association with periventricular leukomalacia and cerebral palsy, and severe hypercapnia is linked with risk of IVH, NEC, BPD and ROP [196]. The consensus view is that modest hypercarbia is reasonable provided the pH is acceptable.

Postnatal Steroids

It is well established, over very many randomised trials and systematic reviews, that postnatal steroids, particularly dexamethasone, have a role in facilitating weaning from MV, and have the potential to reduce BPD, but at the expense of increasing the risk of developmental delay and cerebral palsy as well gastrointestinal perforations. Combining all of the evidence from systematic reviews suggests that the harmful effects outweigh the benefits if dexamethasone is given early (within the first week) [197]. However, beyond seven days, if a baby remains stuck on the ventilator, the risk of BPD (*which is in itself a risk factor for adverse neurodevelopmental outcome*) is sufficiently high to tip the balance in favour of using dexamethasone to facilitate extubation [198]. Roughly for every 10% increase in the risk of BPD, the risk of steroids causing harm decreases by around 3%, with the tipping point for benefits of steroids outweighing harms when the BPD risk is about 60% [199]. For clinicians this means making judgements about the

likelihood of individual infants' risk of BPD, based on their gestation and size, postnatal age, ventilation settings, FiO_2 requirements and X-ray appearances.
Postnatal hydrocortisone has also been used in clinical trials. The Premiloc Trial, which closed before full recruitment, suggested that prophylactic hydrocortisone improved rates of survival without BPD [200], however a systematic review of all trials where hydrocortisone was used before day 15 suggests no overall reduction in BPD [201]. There is heterogeneity with more benefit seen in BPD reduction if there is concomitant chorioamnioitis [201] and overall reduced mortality if hydrocortisone is used. Five-year neurocognitive assessments from around 80 infants involved in the original Premiloc trial is reassuring [202]. Early prophylactic initiation of inhaled corticosteroids may have a benefit in BPD reduction, but there are no apparent benefits or side effects with inhaled corticosteroids started later. We would concur with the Cochrane review authors that there is still insufficient evidence to make firm recommendations on how and when to use inhaled budesonide for improving preterm respiratory outcomes [197]. Two large trials have confirmed unequivocally that there is no role for budesonide mixed in surfactant to prevent BPD [122, 123]

Pain and Sedation
Managing neonatal pain and discomfort whilst on mechanical ventilation is important. For elective intubations sedation with an opioid and a muscle relaxant will result in a greater chance of intubation success [203]. Delivery room intubations are usually semi-urgent and not performed under sedation. With ongoing ventilation there is a balance to be struck between keeping babies comfortable and getting them off the ventilator quickly. There is no evidence that routine sedation with opiates or benzodiazepines influences any important outcomes, in particular no evidence of reduction in intraventricular haemorrhages [204]. In cohort studies, overall use of opiates is falling, but with an increase in the use of Dexmedetomidine [205] which although attractive, has not been adequately studied in this population [206]

Recommendations
1. MV should be used in babies with RDS when other methods of respiratory support have failed (**A1**). Duration of MV should be minimised (**B2**).
2. Lung protective modes such as Volume Targeted Ventilation (rather than pressure cycled) should be the first choice when babies with RDS who require MV (**A1**). NAVA ventilation and, if necessary, High Frequency Oscillation Ventilation may be considered (**C2**).
3. When weaning from MV it is reasonable to tolerate a modest degree of hypercarbia provided the pH remains above 7.22 (**B2**). Avoid $pCO_2 < 4.7$ kPa (35 mmHg) when on MV to reduce brain injury (**C1**).
5. INO in preterm babies should be limited to a therapeutic trial for those with hypoxic respiratory failure and documented pulmonary hypertension and stopped if there is no response (**C2**).
4. Caffeine (20 mg/kg loading, 5–10 mg/kg maintenance) should be used to facilitate weaning from MV and prevent BPD (**A1**). Prophylactic caffeine in standard doses should be given to babies < 32 weeks (**B1**)
5. Short tapering course of low-dose dexamethasone should be considered in babies with high risk of death or BPD who remain on MV after 1–2 weeks (**A2**).
6. Opioids should be used selectively when indicated by clinical judgment and evaluation of pain indicators (**D1**). The routine use of morphine or midazolam infusions in ventilated preterm infants is not recommended (**A1**).

Monitoring and Supportive Care

Advances in technological innovation offers a large variety of methods of monitoring physiological variables in the NICU, and although these are an important part of quality care, consideration is needed balancing costs and potential benefits. Pulse oximetry from birth allows titration of oxygen. ECG monitoring in the delivery room allows more rapid determination of heart rate but may not be necessary at every birth. In the NICU there needs to be access to continuous pulse oximetry and ECG monitoring and a means of measuring blood pressure and blood gases. Arterial blood gases are best, and therefore for babies who require frequent blood gases, umbilical or peripheral arterial cannulation is desirable, particularly if there is a need for continuous blood pressure monitoring. Transcutaneous oxygen and CO_2 monitoring may be helpful for trending, as will continuous end tidal CO_2 monitoring, although skin burns with transcutaneous devices and increased ventilator dead space with end tidal monitoring may preclude use in the smallest

infants. Near infra-red spectroscopy has been used for monitoring and intervening in cerebral hypoxia, however evidence that it improves outcomes is lacking [207, 208]. The ability to rapidly measure haematological indices and electrolytes using small blood volumes is essential, as is 24/7 access to radiology, where X-Rays are used to confirm diagnosis of RDS, check the position of lines and tubes and exclude complications such as air leaks. Increasingly point-of-care ultrasound (POCUS) is used as an alternative to X-rays, highlighting the importance of immediate access to portable ultrasound machines within the NICU [209, 210]

Temperature control

Hypothermia in preterm babies is associated with increased mortality and other adverse outcomes and maintenance of a normal body temperature is considered an important quality measure [211]. High ambient delivery room temperature (> 23°C), wrapping in polythene at birth under a radiant warmer with head covering and heating and humidification of inspiratory gases are all important measures used to reduce risk of hypothermia at birth [212]. Immediate skin-to-skin care after birth for preterm infants offers a safe alternative of maintaining body temperature with the benefits of early maternal-infant bonding [213]. After admission infants should be maintained in servo-controlled incubators initially with relatively high humidity, interspersed with periods of skin-to-skin care when it is safe to do so, even in the tiniest infants [214]. Skin-to-skin and kangaroo mother care are now accepted WHO priorities with evidence of improved breast-feeding rates at discharge making further study in randomised trials ethically unfeasible [215].

Antibiotics and antibiotic stewardship

Antibiotics are often started empirically in preterm infants with RDS because spontaneous preterm labour and respiratory distress are also markers for sepsis. However, antibiotics can be harmful, having effects on the neonatal gut microbiome and potentially increasing the risk of subsequent necrotising enterocolitis [216] and BPD [217]. Policies should be in place to reduce antibiotic exposure, using antibiotics only when there are additional risk factors for sepsis and limiting their use to the narrowest spectrum for the shortest possible duration. It is perfectly reasonable not to screen and treat a preterm infant who has been born by planned caesarean section. Once started empirically, antibiotics can be stopped after 24 - 36 hours if cultures are negative and there is no confirmatory laboratory evidence of sepsis [218]

Early Fluids and Nutritional Support

Over the first days after birth immature stratum corneum and a high skin surface area result in high insensible fluid loss, and this, combined with shifts of water from the interstitial to intravascular compartments, can make early fluid management challenging. Fluids are usually started at around 70-80mL/kg/ day and adjusted upwards at rates according to regular assessments of serum electrolytes, fluid balance and weight. Sodium is usually withheld over the first two days [219] and insensible losses minimised by humidification [220]. Parenteral nutrition (PN) should be started soon after admission as enteral feeding is initially limited. Protocols for PN should include at least 1.5g/kg protein and 1-2g/kg lipids from day one increasing to a maximum of 3 – 3.5g/kg amino acid if tolerated [221]. Small amounts (0.5-1.0 mL/kg/hr) of enteral feeding with colostrum can be started on day one. Mothers own milk is the preferred option for initiation of feeding and feeds can be advanced fairly quickly up to 30ml/kg/day without increased risk of NEC if the infant is otherwise stable [222]. For infants between 30- and 32+6-weeks' GA full enteral feeding can be started from day one without increasing risk of NEC [223].

Recommendations

1. Core temperature should be maintained between 36.5 ^{0}C and 37.5 ^{0}C at all times (**C1**).
2. Most babies should be started on intravenous fluids of 70-80 mL/kg/day in a humidified incubator although some very immature babies may need more (**C1**). Fluids must be tailored individually according to serum sodium levels, urine output and weight loss (**D1**).
3. Parenteral nutrition should be started from birth. Amino acids 1.5-2 g/kg/d should be started from day one and quickly built up to 3.0 g/kg/d and not exceed 3.5 g/kg/day (**B2**). Lipids 1-2 g/kg/d should be started from day one and quickly built up to 3.0 g/kg/ day as tolerated (**C2**).
4. Enteral feeding with mother's milk should be started from the first day if the baby is hemodynamically stable (**B2**). Full enteral feeds can be considered for infants ≥30 weeks' GA (**B2**)

5. In infants with RDS, antibiotics should be used judiciously and stopped early when sepsis is ruled out. (**D1**)

Managing Blood Pressure and Perfusion

There are published normative data, roughly correlating to mean blood pressure equating to gestational age in weeks [224], however measured blood pressure does not always correlate well with cardiac output and perfusion, which are more important determinants of wellbeing. Low blood pressure is associated with worse outcomes, but to date there is no evidence that its treatment makes any difference [225]. Thresholds for when to treat low blood pressure in preterm infants are therefore challenging but should include some measure of end organ perfusion such as urine output, evolving acidosis and tissue perfusion. Where possible, bedside haemodynamic assessment using ultrasound should be used rather than rigidly following protocols for treating the blood pressure reading [226]. Multimodal continuous haemodynamic assessment combining pulse oximetry, electric velocimetry and near-infrared spectroscopy oximetry is promising but further research is needed to confirm benefits [227]. Higher postnatal blood pressure is achieved with antenatal steroids, delayed cord clamping, postnatal hydrocortisone therapy and avoiding invasive mechanical ventilation. Saline boluses should be avoided, as when used for hypotension in extremely preterm infants they do not increase blood pressure but rather decrease lung compliance and increased MV pressure requirements during and after the bolus infusion [228]. Drug treatments for hypotension include epinephrine, dopamine, dobutamine, milrinone, vasopressin and hydrocortisone with the choice of drug depending on the likely cause of the problem, and this lies outside of the scope of these guidelines [229]. An open (patent) ductus arteriosus (PDA) can also contribute to issues with hypotension. All children are born with a PDA and the vast majority will close spontaneously. However, in the least mature infants, persistence of the PDA can lead to reduced systemic blood flow and risk of pulmonary oedema as the pulmonary vascular resistance falls after birth. Although screening for and treating PDA semi-prophylactically may reduce IVH [230], there is no overall improvement in long term outcomes for this strategy and the consensus at present is that there is no particular advantage for adopting this approach [231]. For symptomatic PDA there is little to choose between Indomethacin, Ibuprofen and Paracetamol in terms of effectiveness in closing the duct, but fewer renal adverse effects with paracetamol [232]. In recent years transcatheter PDA occlusion has become available even for small infants with problematic PDA for whom medical therapy has been unsuccessful [233].
Preterm babies are at risk of anaemia of prematurity and often require top up transfusions to maintain satisfactory Hb concentrations. Two major randomised trials comparing thresholds for intervention have shown no major differences in outcome with more restrictive practice and these have been incorporated into new recommendations for when to intervene with a top-up transfusion taking in to account postnatal age and presence or absence of need for respiratory support *(duplicated below*) [234].

Recommendations

1. Treatment of hypotension is recommended when there is evidence of poor tissue perfusion such as oliguria, acidosis, and poor capillary refill (**C2**). Treatment will depend on the cause.
2. When a decision is made to attempt pharmacologic closure of hemodynamically significant PDA then indomethacin, ibuprofen or paracetamol can be used with a similar efficacy (**A2**). Paracetamol is preferred when there is thrombocytopenia or concerns about renal function (**B2**).
3. Thresholds for red blood cell transfusion in infants can be set to 11, 10, 9 g/dl in weeks 1, 2 and 3 for those on respiratory support and 10, 8.5 and 7 g/dl for those on no (or minimal) respiratory support (**A2**).

Conflict of Interest Statement

Christian P. Speer, Ola D Saugstad and Charles C. Roehr in the past have been consultants to Chiesi Farmaceutici, Parma, the manufacturer of an animal-derived surfactant preparation used to treat RDS and a caffeine product for treatment of apnea of prematurity. Virgilio Carnielli is a member of the Chiesi Farmaceutici Advisory Board. Arjan te Pas is the inventor of the Concord Neonatal Resuscitation Trolley but has no financial relationship with Concord Neonatal. Professors Christian Speer and Ola Saugstad are joint Chief Editors of Neonatology. Prof. Mikko Hallman, Prof. Katrin Klebermass-Schrehof, Dr Anna Lavizzari, Prof Arjan te Pas, Prof Charles C Roehr, Prof Ola Didrik Saugstad, Prof Maximo Vento and Prof Christian P Speer were members of the journal's Editorial Board at the time of submission.

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Author Contributions

Dr. David G Sweet was responsible for drafting and revising the manuscript. Profs Gerry HA Visser and Mikko Hallman prepared the first draft of the Prenatal Care section and assisted with subsequent revisions. Profs Katrin Klebermass-Schrehof and Arjan te Pas performed literatures searches and early drafts of the delivery room stabilisation section as well as overall manuscript revisions. Profs Christian P Speer, Charles C Roehr and Dr David Sweet performed literature searches and early drafts of the Surfactant Therapy section as well as overall manuscript revisions. Profs Ola Saugstad and Maximo Vento performed literature searches and provided early drafts of the Oxygen beyond stabilization section as well overall manuscript revisions. Profs Gorm Greisen, Charles C Roehr and Anna Lavizzari provided early drafts of the Non-invasive respiratory support section as well as overall manuscript revisions. Profs Eren Ozek and Arjan te Pas provided literature searches and early drafts of the mechanical ventilation section. Profs Umberto Simeoni and Virgilio Carnielli and Eren Ozek provided literature searches and early drafts of the supportive care section as well as overall manuscript revisions.

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Table 1: Representations of quality of evidence and strength of recommendations

Quality of Evidence	
High Certainty	A
Moderate Certainty	B
Low Certainty	C
Very Low Certainty	D
Strength of Recommendation	
Strong Recommendation	1
Weak or conditional Recommendation	2