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European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants – 2013 Update

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Key Words

Antenatal steroids · Continuous positive airway pressure · Evidence-based practice · Hyaline membrane disease · Mechanical ventilation · Oxygen supplementation · Patent ductus arteriosus · Preterm infant · Respiratory distress syndrome · Surfactant therapy · Thermoregulation

Abstract

Despite recent advances in the perinatal management of neonatal respiratory distress syndrome (RDS), controversies still exist. We report updated recommendations of a European Panel of expert neonatologists who developed consensus guidelines after critical examination of the most up-to-date evidence in 2007 and 2010. This second update of the guidelines is based upon published evidence up to the end of 2012. Strong evidence exists for the role of antenatal steroids in RDS prevention, but it is still not clear if the benefit of repeated courses on respiratory outcomes outweighs the risk of adverse outcomes in the short and long term. Many practices involved in preterm neonatal stabilization at birth are not evidence based, including oxygen administration and positive pressure lung inflation, and they may at times be harmful. Surfactant replacement therapy is crucial in the management of RDS but the best preparation, optimal dose and timing of administration at different gestations is not completely clear. In addition, use of very early continuous positive airway pressure (CPAP) has altered the indications for prophylactic surfactant administration. Respiratory support in the form of mechanical ventilation may be lifesaving but can cause lung injury, and protocols should be directed at avoiding mechanical ventilation where possible by using non-invasive respiratory support such as CPAP. For babies with RDS to have best outcomes, it is essential that they have optimal supportive care, including maintenance of normal body temperature, proper fluid management, good nutritional support, appropriate management of the ductus arteriosus and support of the circulation to maintain adequate tissue perfusion.

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These updated guidelines contain new evidence from recent Cochrane reviews and medical literature since 2010. A new grading system for evaluating the evidence (GRADE) has been adopted. Many of the previous recommendations regarding early surfactant and continuous positive airway pressure are now more firmly evidence based. The section on delivery room stabilization has been considerably expanded. Oxygen therapy after stabilization remains somewhat controversial but until more evidence is available oxygen saturation should not target ranges below 90%. Supportive care remains vitally important for extremely preterm infants. The Miscellaneous section has been shortened.

Introduction

Neonatal respiratory distress syndrome (RDS) is a condition of pulmonary insufficiency that in its natural course commences at or shortly after birth and increases in severity over the first 2 days of life. Clinically, RDS presents with early respiratory distress comprising cyanosis, grunting, retractions and tachypnea. Respiratory failure may develop, indicated by blood gas analysis, and the diagnosis can be confirmed on chest X-ray with a classical 'ground glass' appearance and air bronchograms. If left untreated death may occur from progressive hypoxia and respiratory failure. In survivors resolution begins between 2 and 4 days. RDS is due to a deficiency of alveolar surfactant along with structural immaturity of the lung and it is mainly, but not exclusively, a disease of preterm babies. However, defining RDS is difficult when prophylactic surfactant and very early continuous positive airway pressure (CPAP) are used. The Vermont Oxford Neonatal Network definition requires that babies have a PaO_2 <50 mm Hg (<6.6 kPa) in room air, central cyanosis in room air or need for supplemental oxygen to maintain PaO_2 >50 mm Hg (>6.6 kPa), as well as the classical chest X-ray appearances. With modern early management this classical definition of RDS may not be achieved and making the diagnosis on the basis of having administered surfactant may be an overestimate. The EuroNeoNet figures for 2010 show an incidence of 92% at 24–25 weeks' gestation, 88% at 26–27 weeks, 76% at 28–29 weeks and 57% at 30–31 weeks [1]. Recent large clinical trials show that when managed with early CPAP babies of 26–29 weeks can be managed without intubation or surfactant about 50% of the time [2].

Table 1. Levels of evidence and grades of recommendation

Levels of evidence	
1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews or RCTs with a high risk of bias
2++	High-quality systematic reviews of case control or cohort studies High-quality case control or cohort studies with a very low risk of confounding bias
2+	High quality case control or cohort studies with a low risk of confounding bias
2–	Well-conducted case control or cohort studies with a high risk of confounding bias
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion
Grades of recommendation: GRADE	
A	At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating consistency of results or Extrapolated evidence from studies such as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating 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+

GRADE = Grading of recommendations assessment, development and evaluation [5]; RCT = randomized controlled trial.

The aim of management of RDS is to provide interventions that will maximize survival whilst minimizing potential adverse effects. Over the past 40 years many strategies and therapies for prevention and treatment of RDS have been developed and tested in clinical trials; many of these have now been subjected to systematic reviews. This document updates the previous two guidelines published in 2007 [3] and 2010 [4] after critical examination of the most up-to-date evidence available in late 2012.

The levels of evidence and grades of recommendation used are shown in table 1.

Prenatal Care

Interventions to prevent RDS should begin before birth and involve both paediatricians and obstetricians as part of the perinatal team. Often there is prior warning of impending preterm delivery, allowing time for interventions to be considered including in utero (maternal) transfer where appropriate. Ultrasound examination of cervical length and testing for the presence of fetal fibronectin in vaginal secretions can help to predict the risk of preterm birth [6]. Preterm babies at risk of RDS should be born in centres where appropriate skills are available for stabilization and ongoing respiratory support, including intubation and mechanical ventilation (MV) if indicated. Long-term health outcomes for extremely preterm babies are better if they receive their initial neonatal care in tertiary units [7]. Preterm delivery can be delayed by using antibiotics in the case of preterm, prelabour rupture of the membranes, although co-amoxiclav should be avoided if possible because of an association with an increased risk of necrotizing enterocolitis (NEC) [8]. Magnesium sulphate given to women at risk of imminent preterm birth has been shown to reduce the incidence of cerebral palsy [9]. Progesterone supplementation may delay preterm birth in women with a history of previous preterm delivery and those with a short cervix [10]. Tocolytic drugs can be used in the short term to delay birth to allow safe transfer to a perinatal centre and to enable prenatal corticosteroids to take effect [11].

Prenatal steroids given to women with anticipated preterm delivery reduce the risk of neonatal death (relative risk, 0.55; 95% confidence interval, 0.43–0.72; number needed to treat = 9), and the use of a single course of prenatal corticosteroids does not appear to be associated with any significant maternal or short-term fetal adverse effects [12]. Prenatal steroids decrease the risk of RDS and additionally decrease the risk of intraventricular haemorrhage and NEC [12]. Prenatal corticosteroid therapy is recommended in all pregnancies with threatened preterm labour below 34 weeks' gestation. In pregnancies delivering between 34 and 36 weeks prenatal steroids do not appear to improve outcome [13], although when given before elective caesarean section at term they reduce the risk of admission to the neonatal intensive care unit, albeit with a high number needed to treat [14]. The optimal treatment to delivery interval is more than 24 h and less than 7 days after the start of steroid treatment [12]. Beyond 14 days after administration the benefits of antenatal steroids are diminished [15]. A single repeat course of antenatal betamethasone given a week after the first course to women with threatened preterm labour reduces RDS and other short-term health problems, although birth weight is reduced [16]. Effects of multiple courses of steroids on fetal growth have raised concerns about recommending more than a single additional rescue course until further long-term studies are completed [17].

Recommendations

(1) Women at high risk of very preterm birth should be transferred to perinatal centres with experience in management of RDS (C).
(2) Clinicians should offer a single course of prenatal corticosteroids to all women at risk of preterm delivery from about 23 weeks up to 34 completed weeks' gestation (A).
(3) A second course of antenatal steroids may be appropriate if the first course was administered more than 2–3 weeks earlier and the baby is <33 weeks' gestation when another obstetric indication arises (A).
(4) Antenatal steroids should also be considered for women undergoing a caesarean section prior to labour up to term (B).
(5) Antibiotics should be given to mothers with preterm prelabour rupture of the membranes as this reduces the risk of preterm delivery (A).
(6) Clinicians should consider short-term use of tocolytic drugs to allow completion of a course of prenatal corticosteroids and/or in utero transfer to a perinatal centre (B).

Delivery Room Stabilization

Babies with surfactant deficiency have difficulty achieving adequate functional residual capacity and maintaining alveolar aeration. Traditionally many preterm babies had the umbilical cord cut immediately to facilitate rapid transfer to an overhead warmer where they had initial respiratory support with positive pressure lung inflation, often using 100% oxygen with the aim of achieving visible chest lift and a 'pink baby'. Many of these routine practices have been recently challenged in clinical trials, with modern guidelines advocating a gentler approach to initial respiratory support [18]. The term stabilization is preferred to resuscitation for the vast majority of very preterm infants.

The practice of rapid cord clamping has been questioned. There is evidence supporting a clinical benefit of delayed umbilical cord clamping (30–60 s) in preterm infants [19]. About half of the blood volume of preterm babies is contained in the placenta, and delaying cord clamping can result in an increase in blood volume, particularly after vaginal birth. Meta-analysis of fifteen trials of delayed cord clamping in preterm babies showed that this practice results in higher haematocrit, less need for later transfusion, less NEC and an almost 50% reduction in

intraventricular haemorrhage [20]. A large multicentre trial is underway to determine if this practice genuinely improves short- and long-term outcome [21]. Umbilical cord milking in preterm babies of 24–33 weeks' gestation also results in similar effects on haemoglobin (Hb) levels to delaying cord clamping by 30 s [22].

Reducing hypothermia in babies less than 28 weeks' gestation can be achieved by performing initial stabilization and transfer to the neonatal intensive care unit inside a polyethylene bag or wrap under a radiant warmer [23]. A recent trial comparing this method with or without the addition of an exothermic mattress showed that the mattress increased the risk of overheating [24]. Heating and humidifying the gases used for stabilization may also help to preserve body temperature [25]. The temperature of the delivery room environment is also very important.

It is now established that stabilization with 100% oxygen compared with ambient air is associated with increased mortality in term and near-term newborn babies [26]. Pure oxygen may also be harmful to preterm infants, and current guidelines suggest titrating supplemental oxygen with a blender aiming for saturations that correspond to the normal incremental increase in saturation that occurs after birth [18, 27]. During the transitional phase after birth, saturations measured by pulse oximetry on the right hand should rise gradually from about 60 to 80% over 5 min, reaching 85% and above by about 10 min after birth [28]. When using CPAP from birth in spontaneously breathing preterm babies, normal transitional saturations can be achieved in many without supplemental oxygen [29]. Babies of less than 32 weeks' gestation can in most cases be stabilized starting with 21–30% inspired oxygen concentration, increasing only if persistently bradycardic or cyanosed [30, 31]. Large multicentre trials such as the To2rpido Trial and PRESOX are currently underway to determine if initiation of stabilization of preterm babies in 100 or 60% oxygen versus room air influences long-term outcome [32].

Uncontrolled tidal volumes, either too large or too small, are also detrimental to the immature lung [33, 34]. Applying lung protective strategies right from the initiation of breathing is recommended. The majority of preterm babies are not apnoeic and routine use of positive pressure breaths (bagging) is probably inappropriate [35]. Provision of controlled early CPAP with the ability to provide additional controlled inflations is now the main means of providing safe stabilization of preterm babies immediately after birth, reducing the need for MV and surfactant treatment [36, 37]. CPAP can be delivered via a face mask or a shortened endotracheal tube taped into the nasopharynx [38]. T-piece devices enable a controlled delivery of a set background CPAP with a measured peak inspiratory pressure. If lung inflation is needed a single sustained inflation of about 25 cm H_2O for about 15 s may be better than repeated manual inflations, although more research is needed for this intervention [39]. Self-inflating bags do not require a pressurized gas supply to deliver air flow but cannot deliver CPAP, and the peak inspiratory pressure cannot be controlled beyond the use of the safety valve, which is usually set at about 40 cm H_2O. Flow-inflating bags cannot deliver accurate CPAP and even in experienced hands produce variable gas volumes during lung inflation. Only a minority of babies should require delivery room intubation. If intubation is required, the correct placement of the endotracheal tube can be quickly verified using a colorimetric CO_2 detection device before administering surfactant and starting MV.

Recommendations

(1) If possible delay clamping of the umbilical cord for at least 60 s with the baby held below the mother to promote placento-fetal transfusion (A).

(2) Oxygen for resuscitation should be controlled by using a blender. A concentration of 21–30% oxygen is appropriate to start stabilization and adjustments up or down should be guided by applying pulse oximetry to the right wrist from birth to give information on heart rate and saturation (B).

(3) In spontaneously breathing babies stabilize with CPAP of at least 5–6 cm H_2O via mask or nasal prongs (A).

(4) Intubation should be reserved for babies who have not responded to positive pressure ventilation via face mask (A). Babies who require intubation for stabilization should be given surfactant (A).

(5) Plastic bags or occlusive wrapping under radiant warmers should be used during stabilization in the delivery suite for babies <28 weeks' gestation to reduce the risk of hypothermia (A).

(6) Babies stabilized under a radiant warmer should be servo-controlled within 10 min to avoid overheating (B).

Surfactant Therapy

Surfactant therapy has revolutionized neonatal respiratory care. Most aspects of its use have been tested in multicentre randomized controlled trials, many of which have been subjected to systematic reviews. Surfactant therapy, whether given prophylactically [40] or as rescue therapy [41] to babies with or at risk of developing RDS, reduces the risk of pneumothorax (pulmonary air leak) and neonatal death. Clinical trials have focused on determining the optimal dose, the timing of dosing, the best

Table 2. Surfactant preparations licensed in Europe in 2013

Generic name	Trade name	Source	Manufacturer	Dose (volume)
Beractant	Survanta®	bovine	Ross Laboratories (USA)	100 mg/kg/dose (4 ml/kg)
Bovactant	Alveofact®	bovine	Lyomark Pharma (Germany)	50 mg/kg/dose (1.2 ml/kg)
Poractant alfa	Curosurf®	porcine	Chiesi Farmaceutici (Italy)	100–200 mg/kg/dose (1.25–2.5 ml/kg)

method of administration and the best surfactant preparation. Many of the initial studies were conducted in an era of low antenatal steroid and CPAP use. Since the 2010 European Guidelines were reported several important studies have been published that have re-evaluated the role of surfactant prophylaxis in the current era of early non-invasive respiratory support.

Surfactant Dosing

An experienced neonatal resuscitation/stabilization team is essential for surfactant administration. At least 100 mg/kg of phospholipid is required [42], but there are pharmacokinetic and clinical data suggesting that 200 mg/kg has a longer half-life [43] and a better acute response [44]. If surfactant replacement is needed, the earliest possible administration improves survival, but this comes with the caveat that there is no consistently reliable predictive test to determine whether an individual baby is at risk of developing severe RDS and whether the process of intubation itself may be detrimental. For many years surfactant prophylaxis for extremely preterm infants was considered to offer the best chance of survival [45]. More recent clinical trials show that with a policy of early initiation of CPAP and selective surfactant administration rather than routine prophylaxis babies may do better, with some avoiding intubation altogether and reduced rates of death or chronic lung disease in the CPAP group [37, 46, 47]. However, it must be borne in mind that babies in these trials were recruited antenatally and were therefore delivered in optimal condition, with a high rate of antenatal steroid use. These results may not be generalizable to all babies nor to specific situations within individual institutions [48]. There will still be babies who require intubation for stabilization in the delivery suite and these should be given surfactant before the diagnosis of RDS has been confirmed radiologically.

Most clinical trials used bolus instillation via an endotracheal tube as a standard method for surfactant administration, with babies maintained on MV. MV can be avoided by using the 'INSURE' (INtubate – SURfactant – Extubate to CPAP) technique and this method has been shown in randomized trials to reduce the need for MV and subsequent bronchopulmonary dysplasia (BPD) [49, 50]. The earlier the decision is made to use the INSURE technique, the greater the chance of avoiding ventilation, although more surfactant will be used [51]. Sedation needs to be considered for elective intubation but can increase the risk of apnoea and is still an area of considerable debate [52]. More recently techniques have been developed to deliver surfactant intratracheally whilst avoiding traditional intubation by using a fine catheter with the baby spontaneously breathing on CPAP, and these methods have shown promise in terms of achieving a clinical response without passing an endotracheal tube or using MV, although no improved effects on long-term outcome have so far been demonstrated [53, 54]. Surfactant administration is now possible with modern membrane nebulizers and this is being explored as an alternative for babies with RDS managed on CPAP [55].

Following surfactant administration there may, after a variable period of time, be a need for a further dose of surfactant. In randomized trials 2 doses are better than a single dose [56] and a study with poractant alfa showed that up to 3 doses compared to a single dose reduced mortality (13 vs. 21%) and pulmonary air leaks (9 vs. 18%) [57]. It is practical to use a flexible dosing schedule basing the time of repeat doses on the baby's clinical condition and oxygen requirements and there are pharmacokinetic data to support this approach [58]. Repeated use of the INSURE technique may also be suitable for some babies with RDS who are managing on CPAP but have increasing oxygen requirements [59].

Surfactant Preparations

There are several different surfactant preparations that have been licensed for use in neonates with RDS including synthetic (protein-free) and natural (derived from animal lungs) products. The surfactants currently available in Europe are shown in table 2. Natural surfactants are superior to synthetic preparations, containing only phospholipids, at reducing pulmonary air leaks and mortality [60]. Small trials comparing the porcine-derived porac-

tant alfa and the bovine-derived beractant as rescue therapy show more rapid improvements in oxygenation with the former [61, 62]. Overall there is a survival advantage when a 200 mg/kg dose of poractant alfa is compared with 100 mg/kg of beractant or 100 mg/kg poractant alfa to treat RDS [44]. New generation synthetic surfactants containing surfactant protein analogues appear to work better than older synthetic surfactants and are currently undergoing evaluation in clinical trials [63, 64]. Surfactant preparations containing budesonide have also been developed and are undergoing evaluation to determine if the addition of steroid will reduce the incidence of BPD [65].

Recommendations

(1) Babies with RDS should be given a natural surfactant preparation (A).
(2) A policy of early rescue surfactant should be standard but there are occasions when surfactant should be administered in the delivery suite, such as extremely preterm infants in whom the mother has not had antenatal steroids or those who require intubation for stabilization (A).
(3) Babies with RDS should be given rescue surfactant early in the course of the disease. A suggested protocol would be to treat babies <26 weeks' gestation when FiO_2 requirements >0.30 and babies >26 weeks when FiO_2 requirements >0.40 (B).
(4) Poractant alfa in an initial dose of 200 mg/kg is better than 100 mg/kg of poractant alfa or beractant for treatment of RDS (A).
(5) Consider the INSURE technique. More mature babies can often be extubated to CPAP or nasal intermittent positive pressure ventilation (NIPPV) immediately following surfactant, and a clinical judgement needs to be made as to whether an individual baby will tolerate this (B).
(6) A second, and sometimes a third, dose of surfactant should be administered if there is evidence of ongoing RDS such as a persistent oxygen requirement and need for MV (A).

Oxygen Supplementation beyond Stabilization

Excess supplemental oxygen exposure is clearly linked with development of retinopathy of prematurity and to a lesser extent BPD [66, 67]. Fluctuations in oxygen saturation are also associated with an increased incidence of retinopathy of prematurity [68]. Recently several large trials were undertaken to determine if a lower limit of oxygen saturation targeting is efficacious and safe by randomizing babies to targeting saturations of 85–89% or 91–95%. The first of these studies to be published showed the low saturation target group had a halving of the rate of retinopathy of prematurity in survivors but a 4% increase in the risk of mortality [69]. An interim meta-analysis of data from 2,631 babies which included those in the UK, Australian and New Zealand BOOST II trials confirmed this finding, although the increased mortality was only found in those born at less than 27 weeks' gestation [70]. Long-term follow-up data are awaited, but in the meantime it is prudent to recommend maintaining saturations in the higher target range [71].

Recommendations

(1) In preterm babies receiving oxygen, the saturation target should be between 90 and 95% (B).
(2) After giving surfactant a hyperoxic peak should be avoided by rapid reduction in FiO_2 (C).
(3) Fluctuations in SaO_2 should be avoided in the postnatal period (C).

Non-Invasive Respiratory Support

Non-invasive respiratory support can be defined as any form of respiratory support that is not delivered via an endotracheal tube. It includes CPAP, various types of ventilation provided through soft nasal prongs or masks which are collectively called 'nasal intermittent positive pressure ventilation' (NIPPV) and humidified oxygen delivered by high-flow nasal cannulae [72]. These methods are now used if possible as a substitute for MV in babies with RDS as they are less injurious to the lung [73]. The earlier CPAP is applied the greater the chance of avoiding MV, and when applied from birth CPAP reduces the need for surfactant therapy and MV [36, 37, 74], and the need for tertiary transfer of babies with mild RDS may be avoided [75]. CPAP reduces the need for reintubation if applied following extubation from MV and at least 5 cm H_2O pressure appears to be needed to achieve this [76]. There is no evidence to date of any differences in long-term outcomes among the various devices used to provide nasal CPAP [77, 78]. The interface may however be important, with short binasal prongs being better than single longer prongs, and a small study suggested that nasal masks may be best at preventing reintubation [79, 80].

NIPPV has become a popular alternative to CPAP therapy in recent years [72, 73]. There may be important physiological advantages of NIPPV over nasal CPAP [72]. There is considerable heterogeneity in the methods employed to deliver NIPPV. However, three small trials of synchronized NIPPV versus CPAP following extubation suggested that NIPPV reduced the need for reintubation [72, 81] and may be more effective than nasal CPAP in treating apnoea without influencing long-term outcomes [72]. NIPPV has also been used as the primary

mode of providing respiratory support with some evidence of improved respiratory outcome [82, 83]. Synchronizing nasal ventilation with the baby's own respiratory efforts does not appear to influence its effectiveness [84]. The NIPPV trial was a large international multicentre randomized trial powered to study the important outcome of BPD, recruiting 1,009 extremely low birth weight babies, and it showed no difference between babies randomized to NIPPV compared with CPAP [84].

High-flow nasal cannulae have also been used as a feasible alternative to CPAP in preterm babies in some centres despite lack of evidence of efficacy and safety from high-quality randomized controlled trials [85–87]. If being used as an alternative to CPAP, a flow of 2–4 l/min of humidified gas mixture is typically used in babies <1 kg and 4–6 l/min in heavier babies. High-flow nasal cannulae at flow rates >2 l/min will generate an unquantifiable level of positive end-expiratory pressure (PEEP) and this method of non-invasive respiratory support should be properly evaluated compared to CPAP before firm recommendations can be made [87].

Recommendations

(1) CPAP should be started from birth in all babies at risk of RDS, such as those <30 weeks' gestation who do not need MV, until their clinical status can be assessed (A).
(2) The system delivering CPAP is of little importance; however, the interface should be short binasal prongs or mask and a starting pressure of at least 6 cm H_2O should be applied (A). CPAP level can then be individualized depending on clinical condition, oxygenation and perfusion (D).
(3) CPAP with early rescue surfactant should be considered the optimal management for babies with RDS (A).
(4) A trial of NIPPV can be considered to reduce the risk of extubation failure in babies failing on CPAP; however, this may not offer any significant long-term advantages (A).

MV Strategies

The aim of MV is to provide acceptable blood gases with minimum risk of lung injury, haemodynamic impairment and other adverse events such as hypocarbia, which is associated with neurological impairment. Although MV is injurious to the lung, it is necessary in a significant number of preterm babies with RDS who fail on CPAP. MV can be provided by conventional intermittent positive pressure ventilation (IPPV) or high-frequency oscillatory ventilation (HFOV). Modern ventilators with software and flow sensors enable synchronization and control of the tidal volume being delivered. Technique is more important than mode of ventilation, with HFOV and conventional IPPV being equally effective, and the method that is most successful in an individual unit should be employed [88]. HFOV may be useful as a rescue therapy in babies with severe respiratory failure on IPPV in terms of reducing air leaks but may increase the risk of intraventricular haemorrhage [89].

The aim of MV is to stabilize the lung after recruitment to optimal lung volume with adequate PEEP or continuous distending pressure on HFOV to keep the lung open during the whole respiratory cycle. All modes of MV can induce lung injury. Lung injury in the short term can lead to air leak such as pneumothorax or pulmonary interstitial emphysema and in the longer term may result in BPD. To find the optimum PEEP on conventional ventilation each significant incremental change of PEEP should be evaluated by examining responses in FiO_2 and CO_2 levels and observing pulmonary mechanics. The optimum continuous distending pressure on HFOV is about 1–2 cm of H_2O above the closing pressure identified by deterioration of oxygenation during stepwise reductions in airway pressure [90]. Over-distension should be considered if a baby is deteriorating on MV following surfactant administration or any time when an increase of mean airway pressure is followed by increasing oxygen requirement. Hypocarbia should always be avoided as this is associated with increased risks of BPD and periventricular leukomalacia [91, 92]. A strategy of providing synchronized MV with targeted tidal volume appears best at preventing mortality and BPD in mechanically ventilated newborns [93, 94]. An initial set tidal volume of 4–5 ml/kg should be adjusted according to the measured $PaCO_2$ level and the baby's own respiratory drive. The required tidal volume will increase with advancing postnatal age especially in extremely low birth weight infants [95].

When satisfactory gas exchange is achieved and spontaneous respiratory drive is present weaning should be started immediately. Babies with RDS should be aggressively weaned towards extubation to CPAP provided it is clinically safe and they have acceptable blood gases [96]. Extubation may be successful from 6 to 7 cm H_2O mean airway pressure on conventional modes and from 8 to 9 cm H_2O of continuous distending pressure on HFOV, even in the most immature babies. Keeping very preterm babies stable on low-rate MV for longer periods does not improve the chance of successful extubation [97]. Using synchronized ventilation with targeted tidal volume and pressure support enables weaning of peak inspiratory pressure automatically following surfactant therapy and will prevent hypocarbia and lung injury and shorten the duration of MV [98].

There are clear links between MV through an endotracheal tube and subsequent development of BPD and neurodevelopmental sequelae [99]. Several strategies have been employed specifically to improve the success of noninvasive ventilation and shorten the duration of MV, including caffeine therapy, permissive hypercarbia and the use of postnatal steroids

Caffeine Therapy

Methylxanthines have been used for a long time to treat apnoea of prematurity and to facilitate successful extubation from MV. The Caffeine for Apnea of Prematurity (CAP) study addressed the issue of long-term effects of neonatal caffeine therapy by randomizing 2,006 babies <1,250 g birth weight to caffeine or placebo in the first 10 days of life and continuing until the clinician determined that therapy was no longer needed. Babies assigned to caffeine came off ventilation a week earlier than those assigned to placebo, with a corresponding significant reduction in BPD [100]. Follow-up at 18 months also showed improved outcomes for caffeine-treated babies, with reduced combined outcome of death or neurodisability and reduced rates of cerebral palsy and cognitive delay [101]. By 5 years the differences were no longer significant but reassuring that there was no emergence of long-term adverse effects on development [102]. Babies who were on MV and had started caffeine earliest appeared to derive the most benefit [103]. Caffeine should be part of routine care for very preterm babies with RDS to facilitate extubation and reduce BPD [104].

Permissive Hypercarbia

Although clear evidence of long-term benefit is still lacking [105], tolerating higher $PaCO_2$ levels can lead to reduced time on MV and is now accepted practice [106]. Implementation of a ventilation weaning protocol allowing a degree of hypercarbia can result in earlier extubation and overall reduction in the duration of MV [107]. Tolerating pH levels down to 7.22 over the first 5 days and down to 7.20 thereafter was used in this protocol and is widely accepted.

Postnatal Steroids

Management of BPD is outside the remit of this guideline; however, some babies with RDS who require intubation can develop lung injury and inflammation and become dependent on MV. Dexamethasone is effective at facilitating extubation and reducing BPD but is associated with significant long-term adverse effects, including an increased risk of cerebral palsy when used during the first week of life [108, 109]. The greater the risk of BPD, then the more likely it is that benefits of steroids will outweigh risks [110]. Very early steroid treatment and treatment with high doses cannot be recommended. The recommendations of the 2010 American Academy of Pediatrics are that low-dose dexamethasone (<0.2 mg/kg per day) should be considered in babies who remain ventilator dependent after 1–2 weeks of age [111]. There is also evidence from case series that much lower doses of dexamethasone (0.05 mg/kg/day) might be effective in facilitating extubation [112, 113]. Hydrocortisone is also used in some centres to facilitate extubation as it is claimed to have less potential for adverse effects [114].

Recommendations

(1) MV should be used to support babies when other methods of respiratory support have failed (B). Duration of MV should be minimized to reduce its injurious effect on the lung (B).
(2) Targeted tidal volume ventilation should be employed as this shortens duration of ventilation and reduces BPD (A).
(3) HFOV may be useful as a rescue therapy (B).
(4) When weaning from MV it is reasonable to tolerate a moderate degree of hypercarbia, provided the pH remains above 7.22 (B).
(5) Avoid hypocarbia as this is associated with increased risks of BPD and periventricular leukomalacia (B).
(6) Caffeine should be used in babies with apnoea and to facilitate weaning from MV (A). Caffeine should also be considered for babies at high risk of needing MV, such as those <1,250 g birth weight who are managing on non-invasive respiratory support (B).
(7) A short tapering course of low- or very low-dose dexamethasone should be considered to facilitate extubation in babies who remain on MV after 1–2 weeks (A).

Prophylactic Treatment for Sepsis

Congenital pneumonia may mimic RDS and the commonest organism is group B streptococcus, although *Escherichia coli* and other organisms may also be responsible. For this reason it has been considered good practice to screen all babies with RDS by performing blood cultures, as well as looking for other evidence of sepsis such as neutropenia or an elevated C-reactive protein and initiating antibiotic therapy whilst awaiting results. This routine antibiotic therapy approach is debatable as there is no evidence to support it and prolonged empiric antibiotics in preterm babies are associated with adverse outcomes including NEC [115, 116]. In women who are known to be colonized with group B streptococcus, the risk of early onset sepsis can be reduced by administration of intrapartum antibiotic prophylaxis, although there are

concerns about a high risk of bias in published trials and no effect on mortality has yet been demonstrated [117]. At present it would be considered reasonable not to use routine antibiotics in preterm babies with RDS in low-risk cases such as planned delivery by elective caesarean section. For those who are started on antibiotics, the shortest possible course should be used whilst evidence for absence of sepsis is sought [116, 118]. Routine antifungal prophylaxis with fluconazole or nystatin has also been advocated in recent years to reduce the risk of invasive fungal infection in babies <1,000 g birth weight, although the incidence of this complication in most centres is quite low [119, 120].

Recommendations

(1) Antibiotics are often started in babies with RDS until sepsis has been ruled out, but policies should be in place to narrow the spectrum and minimize unnecessary exposure. A common regimen includes penicillin or ampicillin in combination with an aminoglycoside (D). Antibiotics should be stopped as soon as possible once sepsis has been excluded (C).
(2) In units with a high rate of invasive fungal infection prophylaxis with fluconazole is recommended in babies <1,000 g birth weight or ≤27 weeks' gestation, starting on day 1 of life with 3 mg/kg twice weekly for 6 weeks (A).

Supportive Care

For babies with RDS to have the best outcome it is essential that they have optimal supportive care, including maintenance of a normal body temperature, proper fluid management, good nutritional support, and support of the circulation to maintain adequate blood pressure and tissue perfusion.

Temperature, Fluid and Nutritional Management

Radiant warmers can be used for initial stabilization in the delivery suite and for accessibility in the neonatal intensive care unit. However, in comparison with incubators, increased insensible water losses occur even if a heat shield is used and the duration of their use should be kept to a minimum [121]. In preterm babies in incubators the use of a servo-controlled skin temperature at 36.5°C decreases neonatal mortality [122]. Preterm babies should be nursed in incubators with high relative humidity (60–80%) to reduce insensible water loss, although there is a paucity of data from clinical trials and a wide variation in practice amongst units [123]. Increasingly, skin-to-skin contact and kangaroo care are being utilized as a means of maintaining temperature to maximize the maternal-infant bonding experience, even in babies on MV [124, 125].

In neonatal care, fluid management is important but does not influence the course of RDS. Most protocols include a fixed early fluid intake regimen with progressively increasing volumes over the first few days supplemented with individualized management, considering fluid balance, weight change and serum electrolyte levels. Modest restriction of fluid intake increases early weight loss but has a positive effect in terms of reducing persistent ductus arteriosus (PDA) and NEC [126]. There is no evidence to support the use of diuretics in RDS [127]. A postnatal weight loss is expected over the first few days but can be influenced by early nutritional management.

Intensive nutrition should be initiated from birth as this is known to reduce postnatal weight loss and minimize longer-term postnatal growth restriction. Initially, enteral feeding volumes will be limited, so nutrients should be given as parenteral nutrition to provide enough energy and amino acids to prevent a negative balance and to promote early growth by increasing protein synthesis and nitrogen retention [128–131]. As early as possible, minimal enteral or 'trophic' feeding, using 10–20 ml/kg/day of breast milk, should be provided to enhance maturation and function of the gastrointestinal tract. Cochrane reviews show no increase in the risk of NEC with trophic feeding, earlier initiation of feeding or more rapid advancement of feeds [132–134]. If the mother's own milk is not available then donor breast milk may be better than formula for initiation of feeding as it reduces the risk of NEC [135].

Recommendations

(1) Body temperature should be maintained at 36.5–37.5°C at all times (C).
(2) Most babies should be started on intravenous fluids of 70–80 ml/kg/day while being kept in a humidified incubator, although some very immature babies may need more (D).
(3) Fluids must be tailored individually according to serum sodium levels and weight loss (D).
(4) Sodium intake should be restricted over the first few days of life and initiated after the onset of diuresis with careful monitoring of fluid balance and electrolyte levels (B).
(5) Parenteral nutrition should be started on day 1 to avoid growth restriction and quickly increased to 3.5 g/kg/day of protein and 3.0 g/kg/day of lipids as tolerated (C).
(6) Minimal enteral feeding should also be started from the first day (B).

Managing Blood Pressure, Perfusion and Patent Ductus Arteriosus

Low systemic blood flow and treatment for hypotension are important predictors of poor long-term outcome [136, 137]. In preterm newborns blood pressure

Table 3. Drugs used for treating hypotension in preterm infants

Drug	Dose	Comment	Grade of evidence
0.9% saline	10 ml/kg	if hypovolemia is confirmed	D
Dopamine	2–10 μg/kg/min	usually first line	B
Dobutamine	2–20 μg/kg/min	may be a better choice if myocardial dysfunction is suspected	D
Epinephrine	0.01–0.05 μg/kg/min		D
Hydrocortisone	1 mg/kg 8 hourly	usually as third line in refractory hypotension	B

and systemic blood flow are not closely correlated, especially during the transitional circulation in the first 3 days of life [138, 139]. Cerebral blood flow measurements are similar in well hypotensive compared to normotensive extremely low birth weight infants [140]. There is a lack of data to determine what normal acceptable blood pressure values should be but, as a guide, many clinicians aim to maintain the mean arterial pressure above the gestational age in weeks [141]. There is a move to assess systemic blood flow more accurately using a combination of clinical examination and functional echocardiography to determine if low blood pressure is affecting tissue perfusion and thus help to determine if treatment for hypotension is needed [137, 138, 141]. Low systemic blood flow and hypotension during RDS may be related to hypovolemia, large left-to-right ductus or atrial shunts, or myocardial dysfunction. Knowing the cause can indicate the most appropriate treatment. Early hypovolemia can be minimized by delaying cord clamping. The practice of saline boluses has been questioned as the bolus is rapidly distributed to the extravascular space and may increase lung oedema [142]. Volume expansion with 10–20 ml/kg of normal saline, rather than colloid, can be considered when hypovolemia has been confirmed by echocardiography or if the cause is not clearly established [143, 144]. Dopamine is more effective than dobutamine to treat hypotension in preterm infants in terms of short-term outcome [145], although dobutamine may be a more rational choice in the setting of myocardial dysfunction and low systemic blood flow**.** Hydrocortisone may also be used for the treatment of hypotension after conventional treatment has failed [146]. More studies are planned to define thresholds for intervention in neonatal hypotension and to find out how treatment of hypotension influences long-term outcomes [147]. Milrinone does not appear to improve perfusion in this population [148]. Drugs used to support blood pressure in neonates are shown in table 3.

Maintenance of an adequate circulating haemoglobin (Hb) concentration is also important. Delaying cord clamping will improve early haematocrit. Normative values of all haematological indices calculated from large databases have recently been published [149]. The PINT trial showed that targeting Hb concentration 1–2 g/dl lower in extremely low birth weight infants resulted in less need for blood transfusion and no difference in short-term outcome [150]. However, long-term differences in cognitive outcomes have led to concerns about restrictive Hb protocols and more research is needed [151, 152].

PDA may provide clinical problems for very preterm babies with RDS. There is no convincing evidence at present to make meaningful recommendations for when to treat PDA, but cyclooxygenase inhibitors (indomethacin or ibuprofen) should be considered when there is poor perfusion, a large left-to-right shunt and a baby for whom weaning from respiratory support is problematic. Prophylactic indomethacin will reduce PDA and intraventricular haemorrhage but there is no difference in long-term outcome [153]. The efficacy of indomethacin and ibuprofen are equivalent, although ibuprofen may have fewer adverse effects [154]. Oral ibuprofen is also effective for PDA closure [155]. There is an observed association between surgical ligation and an increased risk of long-term adverse effects; however, it is not clear if this is a direct result of surgery or due to complications incurred whilst waiting for it [156].

Recommendations

(1) Treatment of arterial hypotension is recommended when it is confirmed by evidence of poor tissue perfusion (C).
(2) Hb concentration should be maintained within normal limits (D). A suggested Hb threshold for babies on respiratory support is 12 g/dl in week 1, 11 g/dl in week 2 and 9 g/dl beyond 2 weeks of age.
(3) If a decision is made to attempt therapeutic closure of the PDA then indomethacin or ibuprofen have been shown to be equally efficacious, although there is less evidence of transient renal failure or NEC with ibuprofen (A).

Table 4. Summary of recommendations

Prenatal care	– Preterm babies at risk of RDS should be born in centres where appropriate care, including MV, is available – If possible, birth should be delayed to allow the maximum benefit of prenatal corticosteroid therapy
Delivery room stabilization	– Aim to delay cord clamping at birth by at least 60 s – Stabilize baby in a plastic bag under a radiant warmer to prevent heat loss – Stabilize gently, avoiding excessive tidal volumes and exposure to 100% oxygen, using pulse oximetry as a guide provided there is an adequate heart rate response – For extremely preterm infants, consider intubation in delivery suite for prophylactic surfactant administration if antenatal steroids have not been given; for most babies, CPAP should be initiated early
Respiratory support and surfactant	– Natural surfactants should be used and given as early as possible in the course of RDS – Repeat doses of surfactant may be required if there is ongoing evidence of RDS – More mature babies can often be extubated to CPAP or NIPPV immediately following surfactant, and a judgement needs to be made as to whether an individual baby will tolerate this – For those who require MV, aim to ventilate for as short a time as possible, avoiding hyperoxia, hypocarbia and volutrauma – Caffeine therapy should be used to minimize need for and duration of ventilation – Babies should be maintained on CPAP or NIPPV in preference to ventilation if possible
Supportive care	– Antibiotics should be started until sepsis has been ruled out unless the risk of infection is low, for example after an elective caesarean section – Maintain body temperature in the normal range – Careful fluid balance is required with early aggressive nutritional support using parenteral nutrition whilst enteral feeding is being established – Blood pressure should be monitored regularly, aiming to maintain normal tissue perfusion, if necessary using inotropes – Consideration should be given to whether pharmacological closure of the ductus arteriosus is indicated

Miscellaneous Considerations

Although RDS is primarily a disease of preterm babies, it can occur in those born close to or at term. RDS should be considered as a differential diagnosis in any baby with early respiratory distress, and surfactant therapy considered as part of management [157]. In rare cases, babies with RDS may suffer from genetic conditions such as surfactant protein-B or ABCA3 deficiency which are difficult to manage and beyond the scope of these guidelines [158].

Surfactant is also sometimes given in situations other than RDS. Preterm babies with RDS occasionally develop massive pulmonary haemorrhage, particularly in the presence of a large PDA. Additional surfactant replacement seems to improve oxygenation, although there are no good randomized trials to support this [159]. Surfactant also appears to improve oxygenation in babies with congenital pneumonia, although the response is slower, more doses may be required and no proper randomized controlled trials for this indication have been performed [160, 161]. Surfactant therapy has also been administered late in the course of respiratory disease in babies with evolving BPD and acute improvements in oxygenation occur, but the effect is not sustained [162].

In contrast to term infants, several large randomized controlled studies of inhaled nitric oxide in preterm babies with respiratory distress, hypoxic respiratory failure or early evolving BPD have failed to demonstrate clear benefits in terms of survival or reduced BPD [163, 164]. Until further studies have been performed, inhaled nitric oxide cannot be recommended for the prevention of BPD in preterm infants.

Recommendations

(1) Elective caesarean section in low-risk pregnancies should not be performed before 39 weeks' gestation (B).
(2) Inhaled nitric oxide therapy is not beneficial in the management of preterm babies with RDS (A).
(3) Surfactant therapy can be used to improve oxygenation following pulmonary haemorrhage but there may be no long-term benefits (C).
(4) Surfactant replacement for evolving BPD leads to only short-term benefits and cannot be recommended (C).

Conclusion

The recommendations discussed in detail on prenatal care, delivery room stabilization, respiratory support and surfactant, and supportive care are summarized in table 4. These recommendations are based on evidence available from clinical trials, systematic reviews and experience at the end of 2012. They should be updated in 3 years, that is, in 2016.

Disclosure Statement

A European panel of experts was convened under the auspices of the European Association of Perinatal Medicine to update evidence-based guidelines on the management of RDS. The guidelines were prepared using evidence-based methods as summarized in table 1. Henry Halliday and Christian Speer are consultants to Chiesi Farmaceutici, Parma, the manufacturers of a leading natural surfactant preparation used to treat RDS and a caffeine product for treating apnoea of prematurity. Ola Saugstad and Virgilio Carnielli are members of the Chiesi Farmaceutici Advisory Board. Henry Halliday and Christian Speer are joint Chief Editors of *Neonatology*.

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