Consensus Guidelines

Neonatology
formerly Biology of the Neonate

Neonatology 2010;97:402–417
DOI: 10.1159/000297773

Published online: June 10, 2010

European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants – 2010 Update

David G. Sweet[a] Virgilio Carnielli[b] Gorm Greisen[c] Mikko Hallman[d] Eren Ozek[e] Richard Plavka[f] Ola D. Saugstad[g] Umberto Simeoni[h] Christian P. Speer[i] Henry L. Halliday[j]

[a]Regional Neonatal Unit, Royal Maternity Hospital, Belfast, UK; [b]Dipartimento di Neonatologia, Ospedale Universitario di Ancona, Università Politecnica delle Marche, Ancona, Italy; [c]Department of Neonatology, Rigshospitalet and University of Copenhagen, Copenhagen, Denmark; [d]Department of Pediatrics, Institute of Clinical Medicine, Oulu University Hospital, University of Oulu, Oulu, Finland; [e]Department of Pediatrics, Marmara University Medical Faculty, Istanbul, Turkey; [f]Division of Neonatology, Department of Obstetrics and Gynecology, General Faculty Hospital and 1st Faculty of Medicine, Charles University, Prague, Czech Republic; [g]Department of Pediatric Research, Rikshospitalet Medical Center, Faculty of Medicine, University of Oslo, Oslo, Norway; [h]Service de Néonatologie, Hôpital de la Conception, Assistance Publique – Hopitaux de Marseille, Marseille, France; [i]Department of Pediatrics, University Children's Hospital, Würzburg, Germany; [j]Department of Child Health, Queen's University Belfast and Royal Maternity Hospital, Belfast, UK

These updated guidelines contain new evidence from recent Cochrane reviews and the medical literature since 2007. Many of the previous recommendations regarding early surfactant and CPAP are now more firmly evidence-based. The section on delivery room stabilisation has been considerably expanded. There are new recommendations on delaying umbilical cord clamping and a new section has been added on avoiding or reducing duration of mechanical ventilation, including recommendations on caffeine therapy, nasal ventilation, permissive hypercapnia and the role of newer ventilator modalities. A new 'miscellaneous' section has also been added covering aspects of RDS management that arise infrequently.

Key Words
Antenatal steroids · Continuous positive airway pressure · Evidence-based practice · Mechanical ventilation · Oxygen supplementation · Patent ductus arteriosus · 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 the updated recommendations of a European panel of expert neonatologists who had developed consensus guidelines after critical examination of the most up-to-date evidence in 2007. These updated guidelines are based upon published evidence up to the end of 2009. Strong evidence exists for the role of a single course of antenatal steroids in RDS prevention, but the potential benefit and long-term safety of repeated courses are unclear. Many

These guidelines have been endorsed by the European Association of Perinatal Medicine.

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Prof. Henry L. Halliday, MD, FRCPE, FRCP, FRCPCH
Perinatal Medicine, Royal Maternity Hospital
Grosvenor Road, Belfast BT12 6BB (UK)
Tel. +44 2890 633 460, Fax +44 2890 236 203
E-Mail h.halliday@qub.ac.uk

Table 1. Grades of recommendation and levels of evidence

Grade of recommendation	Level of evidence
A	At least one high-quality meta-analysis of randomised controlled trials (RCTs) or a sufficiently powered high-quality RCT directly applicable to the target population
B	Other meta-analyses of RCTs or a high-quality systematic review of case-control studies or a low-grade RCT but with a high probability that the relationship is causal
C	A well-conducted case-control or cohort study with a low risk of confounding or bias
D	Evidence from case series, case reports or expert opinion

Modified from SIGN guidelines developer's handbook www.sign.ac.uk/guidelines/fulltext/50/.

practices involved in preterm neonatal stabilisation 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 always clear. Respiratory support in the form of mechanical ventilation may also be lifesaving, but can cause lung injury, and protocols should be directed at avoiding mechanical ventilation where possible by using nasal continuous positive airways pressure or nasal ventilation. For babies with RDS to have best outcomes, it is essential that they have optimal supportive care, including maintenance of a normal body temperature, proper fluid management, good nutritional support, management of the ductus arteriosus and support of the circulation to maintain adequate tissue perfusion.

Introduction

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. If left untreated, death can occur from progressive hypoxia and respiratory failure. In survivors, resolution begins between 2 and 4 days. RDS is due to a deficiency and immaturity of alveolar surfactant along with structural immaturity of the lung and it is mainly, but not exclusively, confined to preterm babies. The incidence increases with decreasing gestation, with EuroNeoStat figures for 2006 showing an incidence of 91% at 23–25 weeks', 88% at 26–27 weeks', 74% at 28–29 weeks', and 52% at 30–31 weeks' gestation [1]. Clinically RDS presents with early respiratory distress comprising cyanosis, grunting, retractions, and tachypnoea. Respiratory failure may develop and is indicated by blood gas analysis. The diagnosis can be confirmed on chest x-ray with a classical 'ground glass' appearance and air bronchograms. 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. However, it is important to note that with modern early management the classical definition of RDS may not be attained.

The aim of management of RDS is to provide interventions that will maximise the number of survivors whilst minimising 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 guidelines published in 2007 [2] after critical examination of the most up-to-date evidence available in late 2009. 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. There is often prior warning of impending preterm delivery, allowing time for interventions to be considered including in utero (maternal)

transfer where appropriate. Surfactant secretion generally increases during labour, therefore elective caesarean section of low-risk fetuses before 39 weeks' gestation should not be performed, as some of them may develop RDS or other respiratory disorders [3]. Preterm babies at risk of RDS should be born in centres where appropriate skills are available for stabilisation and ongoing respiratory support, including intubation and mechanical ventilation (MV). For babies <27 weeks' gestation, the odds of dying within the first year of life are halved if they are born in a hospital that has a level III neonatal intensive care unit (NICU) able to provide such tertiary care [4, 5]. Preterm delivery can be delayed by using antibiotics in the case of preterm, pre-labour rupture of the membranes [6], and tocolytic drugs can be used in the short term to delay birth [7–10] to allow safe transfer to a perinatal centre and to enable antenatal steroids to take effect. Antibiotic choice in the case of ruptured membranes is not clear. Co-amoxiclav (amoxicillin and clavulanic acid) appears to be associated with an increased risk of neonatal necrotising enterocolitis and the Cochrane Review authors suggested erythromycin as a better choice [6]. A recent 7-year follow-up study of babies from the ORACLE trial confirmed that with preterm ruptured membranes there are no differences in long-term adverse outcomes between erythromycin and co-amoxiclav [11], although use of erythromycin in the setting of preterm labour with intact membranes was associated with an increased risk of later functional impairment and cerebral palsy [12].

Antenatal steroids are given to mothers to reduce the risk of neonatal death [relative risk (RR) 0.55; 95% confidence interval (CI) 0.43–0.72; number needed to treat (NNT) 9] and the use of a single course of antenatal steroids does not appear to be associated with any significant maternal or fetal adverse effects [13]. Antenatal steroids decrease the risk of RDS (RR 0.66; 95% CI 0.59–0.73; NNT 11). This effect is limited to those preterm infants whose mothers received the first dose of steroid 1–7 days before birth (RR 0.46; 95% CI 0.35–0.60; NNT 7) [13]. Antenatal steroids additionally decrease the risk of intraventricular haemorrhage and necrotising enterocolitis [13]. Betamethasone and dexamethasone have both been used to enhance fetal lung maturity. Observational cohort studies previously suggested increased rates of cystic periventricular leucomalacia in babies of mothers treated with dexamethasone [14, 15]. However, a recent Cochrane Review suggests less intraventricular haemorrhage with dexamethasone [16], so at present no firm recommendations can be made regarding choice of steroid. Antenatal steroid therapy is recommended in all pregnancies with threatened preterm labour before 35 weeks' gestation. In high-risk pregnancies with planned elective deliveries between 35 and 38 weeks and with documented fetal lung immaturity (amniotic fluid analysis of lecithin-sphingomyelin ratio, phosphatidylglycerol or lamellar bodies), a course of antenatal steroids may also be indicated, although randomised controlled trials have failed to demonstrate significant benefit in late pregnancy [13]. Although a statistically significant reduction in rates of RDS in babies <28 weeks' gestation has not been demonstrated in clinical trials of antenatal steroids, this is probably because of inadequate numbers of very immature babies included in the original studies [13]. Improved neurological outcome has been demonstrated for even the most immature babies [13, 17]. The optimal treatment to delivery interval is >24 h and <7 days after the start of steroid treatment [13].

There is continuing uncertainty over the use of repeated courses of antenatal steroids. Although repeated courses given 7 days after the previous course decreased the risk of RDS in preterm pregnancies [18], babies exposed to repeat steroid courses weigh less and have smaller head circumferences at birth [18, 19]. Long-term follow-up data are just emerging [20, 21] with some studies highlighting concerns about increased rates of cerebral palsy. Recently, antenatal steroid exposure has also been associated with an increase in insulin resistance in later life [22]. The most recent Cochrane Review concludes that further research is needed before repeat courses of antenatal steroids can be routinely recommended [18]. Since this update, another large randomised trial has been published showing early benefits of a rescue course of betamethasone when birth has not occurred after the first course [23]. Multiple pregnancy may be a situation in which a repeat course may offer added benefit [24, 25].

Recommendations

(1) Mothers at high risk of preterm birth should be transferred to perinatal centres with experience in management of RDS (C).
(2) Clinicians should offer a single course of antenatal steroids to all women at risk of preterm delivery from about 23 weeks up to 35 completed weeks' gestation (A).
(3) Antibiotics should be given to mothers with preterm pre-labour rupture of the membranes as this reduces the risk of preterm delivery (A).
(4) Clinicians should consider short-term use of tocolytic drugs to allow completion of a course of antenatal steroids and/or in utero transfer to a perinatal centre (A).
(5) A second course of antenatal steroids should be considered if the risk from RDS is felt to outweigh the uncertainty about possible long-term adverse effects (D). One example where benefit might outweigh the risk is multiple pregnancy (C).

Delivery Room Stabilisation

Babies with surfactant deficiency have difficulty achieving adequate functional residual capacity and maintaining alveolar aeration. Traditionally many preterm babies have the umbilical cord cut immediately to facilitate rapid transfer to a warmer environment where they are resuscitated with bag and mask ventilation, often using 100% oxygen with the aim of achieving visible chest lift and a 'pink' baby [26]. Many of these routine practices have recently been challenged [27].

The practice of rapid cord clamping has been questioned. About half of the blood volume of preterm babies is contained in the placenta, and delaying cord clamping for 30–45 s can result in an 8–24% increase in blood volume, particularly after vaginal birth [28]. Meta-analysis of seven trials of delayed cord clamping showed that this practice, with or without simultaneous maternal oxytocin administration, results in higher haematocrit, less need for later transfusion and a reduction in intraventricular haemorrhage [29, 30].

At present the optimal oxygen saturation (SaO_2) during stabilisation of preterm infants is not known, but there is now evidence that resuscitation with 100% oxygen compared with ambient air is associated with increased mortality in term and near-term newborn babies [31]. Pure oxygen may also be harmful to preterm infants, with a 20% decrease in cerebral blood flow observed at 2 h of age and worse alveolar/arterial oxygen gradients in babies resuscitated with oxygen compared to air [32]. Biochemical evidence of oxygen toxicity persists for days even after very short periods of oxygen supplementation at birth [33]. For babies <32 weeks only four small studies have been published [33–36] and of these only three were randomised trials. Room air will often not be sufficient for stabilisation of preterm babies [34], however, with the use of pulse oximetry as a guide, babies <32 weeks' gestation can in most cases be stabilised starting with about 30% inspired oxygen concentration [36]. Routine use of 100% oxygen is no longer appropriate and oxygen-air blenders should be available in delivery suites to allow titration of oxygen delivery according to the condition of the baby. Normative data for oxygen saturations measured by pulse oximetry during transition after birth are now available and clinicians should not intervene immediately during this phase provided there is an adequate heart rate. During the transitional phase after birth, saturations should rise gradually from about 60 to 80% over 5 min, reaching 85% and above by about 10 min after birth [37–39]. Oximetry may identify babies outside this range and help guide inspired oxygen delivery.

It is also now clear that uncontrolled tidal volumes at birth, either too large or too small, may be detrimental to the immature lung [40, 41]. Routine use of positive pressure breaths (bagging) is probably inappropriate for spontaneously breathing preterm babies. Delivery room provision of a means of lung inflation has changed over recent years. Traditional reliance on self-inflating bags, or flow-inflating 'anaesthetic' bags has now largely been superseded by the use of T-piece devices. These enable a controlled delivery of a set background continuous positive airways pressure (CPAP) with a measured peak inspiratory pressure (PIP) during occlusion of the T-piece. Self-inflating bags do not require a pressurised gas supply to deliver air flow, but cannot deliver CPAP and the PIP 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 [42]. Provision of controlled early CPAP is now the main means of providing safe stabilisation of preterm babies immediately after birth and devices that can provide this, such as the Neopuff® infant resuscitation device, are recommended. Delivery room CPAP reduces the need for mechanical ventilation (MV) and surfactant treatment, although not using surfactant may increase the risk of pneumothorax [43]. A single sustained inflation breath prior to initiation of CPAP is better than repetitive manual inflations in terms of reducing need for early ventilation and subsequent lung injury [44]. Only a minority of babies should require delivery room intubation. These will include babies in whom it has been decided in advance to administer prophylactic surfactant (see later), and those who do not respond to CPAP and gentle controlled inflation breaths via a T-piece device. 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.

During stabilisation all efforts should be made to reduce heat loss to prevent hypothermia since this improves survival [45]. Use of a polyethylene bag or wrap under a radiant warmer will reduce hypothermia during care in the delivery room and transfer to the NICU in infants <28 weeks' gestation, but it is not yet certain if it leads to improved outcome [46].

Recommendations

(1) If possible, delay clamping of the umbilical cord for at least 30–45 s with the baby held below the mother to promote placento-fetal transfusion (A).
(2) Oxygen for resuscitation should be controlled by using an air-oxygen blender. The lowest concentration of oxygen possible should be used during stabilisation, provided there is an adequate heart rate response. A concentration of 30% oxygen is appropriate to start stabilisation and adjustments up or down should be guided by applying pulse oximetry from birth to give information on heart rate (B). Normal saturations during transition immediately after birth in very preterm infants may be between 40 and 60%, reaching between 50 and 80% at 5 min of age and should be >85% by 10 min of age. Exposure to hyperoxia should be avoided during stabilisation (B).
(3) In spontaneously breathing babies start stabilisation with CPAP of at least 5–6 cm H_2O via mask or nasal prongs (B). If breathing is insufficient, consider the use of a sustained inflation breath to recruit the lung rather than intermittent positive pressure breaths (B).
(4) Ventilation with a T-piece device is preferable to a self-inflating, or flow-inflating bag in order to generate appropriate positive end-expiratory pressure (PEEP) (C).
(5) If positive pressure ventilation is needed for stabilisation, aim to avoid excessive tidal volumes by incorporating resuscitation devices which measure or limit the PIP whilst at the same time maintaining PEEP during expiration (D).
(6) Intubation should be reserved for babies who have not responded to positive pressure ventilation or those requiring surfactant therapy (D).
(7) If the baby is intubated, correct positioning of the endotracheal tube should be verified by colorimetric CO_2 detection (D).
(8) Plastic bags or occlusive wrapping under radiant warmers should be used during stabilisation in the delivery suite for babies <28 weeks' gestation to reduce the risk of hypothermia (A).

Surfactant Therapy

Surfactant therapy has revolutionised neonatal respiratory care over the past two decades. Most aspects of its use have been tested in multicentre randomised controlled trials, many of which have been subjected to systematic reviews. It is clear that surfactant therapy, whether given prophylactically [47] or as rescue therapy [48] to babies with or at risk of developing RDS, reduces the risk of pneumothorax (pulmonary air leak) and neonatal death. The trials have focused on determining the optimal dose, the timing of dosing, the best method of administration and the best surfactant preparation, although many of the studies were conducted in an era of low antenatal steroid and CPAP use.

Surfactant Dosing and Redosing

An experienced neonatal resuscitation/stabilisation team is essential for surfactant administration. At least 100 mg/kg of phospholipid is required [49] but there are pharmacokinetic and clinical data suggesting that 200 mg/kg has a longer half-life [50] and better acute response [51]. Most clinical trials have used bolus instillation and this appears to result in better distribution of surfactant. Surfactant prophylaxis in babies of <31 weeks' gestation reduces mortality (RR 0.61; 95% CI 0.48–0.77; NNT 20) and pulmonary air leaks (RR 0.62; 95% CI 0.42–0.89; NNT 50) compared to later rescue surfactant, but may result in some babies being intubated and receiving surfactant unnecessarily [52]. The aim is to treat all babies at risk of developing RDS as early as possible, and this will include babies deemed to be at very high risk who should receive prophylactic therapy in the delivery suite before the diagnosis has been confirmed radiologically. In babies who require surfactant, MV can also be avoided by using the 'INSURE' (INtubate – SURfactant – Extubate to CPAP) technique and this method has been shown in randomised trials to reduce the need for MV and subsequent BPD [53, 54]. Surfactant therapy clearly works better the earlier in the course of RDS it is given. The earlier that the decision is made to give surfactant, the greater the chance of avoiding ventilation, although more surfactant will be used [53–55].

Following surfactant administration there may, after a variable period of time, be a need for a further dose of surfactant. In randomised trials it would appear that two 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]. Previously, rigid dosing protocols were used but it is more practicable 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]. Surfactant therapy beyond the first few days of life has only been studied in a small number of subjects and results in acute responses only with no evidence of any difference in long-term outcome [59].

Surfactant Preparations

There are several different types of surfactant preparation licensed for use in neonates with RDS including synthetic (protein-free) and natural (derived from animal lungs) surfactants (table 2). Natural surfactants are better than synthetic preparations at reducing pulmonary air

Table 2. Surfactant preparations 2010

Generic name	Trade name	Source	Manufacturer	Dose (volume)
Bovactant	Alveofact®	Bovine	Lyomark (Germany)	50 mg/kg/dose (1.2 ml/kg)
BLES[1]	BLES®	Bovine	BLES Biochemicals (Canada)	135 mg/kg/dose (5 ml/kg)
Poractant alfa	Curosurf®	Porcine	Chiesi Farmaceutici (Italy)	100–200 mg/kg/dose (1.25–2.5 ml/kg)
Colfosceril palmitate[1]	Exosurf®	Synthetic	GlaxoSmithKline (USA)	64 mg/kg/dose (5 ml/kg)
Calfactant	Infasurf®	Bovine	ONY Inc. (USA)	105 mg/kg/dose (3 ml/kg)
Surfactant-TA[1]	Surfacten®	Bovine	Tokyo Tanabe (Japan)	100 mg/kg/dose (3.3 ml/kg)
Lucinactant	Surfaxin®	Synthetic	Discovery Labs (USA)	Not licensed
Beractant	Survanta®	Bovine	Ross Labs (USA)	100 mg/kg/dose (4 ml/kg)

[1] Not available in Europe.

leaks (RR 0.63; 95% CI 0.53–0.75; NNT 25) and mortality (RR 0.86; 95% CI 0.76–0.98; NNT 50) [60]. Natural surfactants are therefore the treatment of choice and are the only surfactants available in Europe. Trials comparing the natural bovine surfactants calfactant and beractant showed no difference in outcome when given prophylactically or as rescue therapy [61, 62]. Trials comparing the porcine-derived poractant alfa and the bovine-derived beractant as rescue therapy individually show more rapid improvements in oxygenation with the former [51, 63] and a reduced mortality in one trial [51]. A meta-analysis demonstrated an overall 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 established RDS (RR 0.29; 95% CI 0.10–0.79; NNT 14) [64]. New generation synthetic surfactants are being developed but to date have not been licensed to treat RDS in the newborn [65].

Recommendations

(1) Babies with or at high risk of RDS should be given a natural surfactant preparation (A).
(2) Prophylaxis (within 15 min of birth) should be given to almost all babies of <26 weeks' gestation. Prophylaxis should also be given to all preterm babies with RDS who require intubation for stabilisation (A).
(3) Early rescue surfactant should be administered to previously untreated babies if there is evidence of RDS (A). Individual units need to develop protocols for when to intervene as RDS progresses depending on gestational age and prior treatment with antenatal steroids (D). Poractant alfa in an initial dose of 200 mg/kg is better than 100 mg/kg of poractant alfa or beractant for treatment of moderate to severe RDS (B).
(4) Consider immediate (or early) extubation to non-invasive respiratory support (CPAP or nasal intermittent positive pressure ventilation (NIPPV)) following surfactant administration provided the baby is otherwise stable (B).
(5) A second, and sometimes a third dose of surfactant should be administered if there is ongoing evidence of RDS such as a persistent oxygen requirement and need for MV (A).

Oxygen Supplementation beyond Stabilisation

There is currently no firm evidence to guide optimal oxygen saturation targeting during the acute management of RDS. Beyond the initial stabilisation period, data suggest that oxygen saturation targets in preterm babies receiving supplemental oxygen should be maintained between 85 and 93% and not exceed 95% in order to reduce the risks of retinopathy of prematurity (ROP) and BPD [66–71]. Large studies to determine the potential beneficial effects of reduction of progression of ROP by targeting higher saturations failed to show any improved ophthalmological outcome, however, the babies in higher oxygen had more respiratory symptoms and an increased incidence of chronic oxygen dependency [72, 73]. It seems logical to avoid excess oxygen exposure at any time as there is no reason to believe that babies within the first few days after birth tolerate hyperoxia better than later in life. However, there are at present no data to show what lower limit of oxygen saturation targeting is safe. There are data to suggest that fluctuations in oxygen saturation can be harmful as they are associated with an increased incidence of ROP [74, 75]. Optimal saturation targets will hopefully be determined following completion of current large randomised trials in USA, Canada, Australia, New Zealand and the UK.

Recommendations

(1) In babies receiving oxygen, saturation should be maintained between 85 and 93% (D).
(2) After giving surfactant avoid a hyperoxic peak by rapid reduction in FiO_2 (C).
(3) Avoid fluctuations in SaO_2 in the postnatal period (D).

Role of CPAP in Management of RDS

Nasal CPAP is now used as a substitute for MV to provide respiratory support for many babies with RDS, and some can be managed on CPAP without receiving surfactant treatment [76]. The earlier CPAP is applied, the greater the chance of avoiding MV (RR 0.55; 95% CI 0.32–0.96; NNT 6) [77]. When applied from birth, CPAP reduces the need for surfactant therapy and MV [43], and can potentially reduce the need for tertiary transfer of babies with mild RDS [78]. However, by not using surfactant the baby is exposed to a greater risk of developing a pneumothorax [43, 78]. 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 [79]. There is no evidence to date of any differences in long-term outcomes among the various devices used to provide nasal CPAP [80, 81], but studies have shown that short binasal prongs are a better interface than a single prong reducing the need for reintubation (RR 0.59; 95% CI 0.41–0.85; NNT 5) [82].

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 (D).
(2) Short binasal prongs should be used rather than a single prong as they reduce the need for intubation and a pressure of at least 5 cm H_2O should be applied (A).
(3) The use of CPAP with early rescue surfactant should be considered in babies with RDS in order to reduce the need for MV (A).

Mechanical Ventilation 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 hypocapnia which is associated with neurological impairment. Before surfactant became available, MV was shown to reduce death from RDS [83]. MV can be provided by conventional modes, such as intermittent positive pressure ventilation (IPPV) or high-frequency oscillatory ventilation (HFOV) [84]. The principle of MV is to stabilise the lung after recruitment to optimal lung volume with adequate PEEP or continuing distending pressure (CDP) on HFOV to keep the lung open during the whole respiratory cycle. Technique is more important than mode of ventilation and the method that is most successful in an individual unit should be employed [85]. HFOV may be useful as a rescue therapy in babies with severe respiratory failure on IPPV [86]. Rescue HFOV reduces new pulmonary air leaks (RR 0.73; 95% CI 0.55–0.96; NNT 6) but there are concerns about increased risks of intraventricular haemorrhage [RR 1.77; 95% CI 1.06–2.96; number needed to harm 6] in preterm babies if a lung volume recruitment procedure is not used [86]. 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 can result in BPD. Overdistension should be considered if a baby is deteriorating on MV following surfactant administration or anytime when an increase of mean airway pressure is followed by increasing oxygen need. To find the optimum PEEP on conventional ventilation, each significant incremental change of PEEP should be evaluated by examining responses in FiO_2, CO_2 level and observing pulmonary mechanics. The optimum CDP on HFOV is about 1–2 cm H_2O above the closing pressure identified by deterioration of oxygenation during stepwise reductions in airway pressure during a lung volume recruitment procedure [87]. Hypocapnia should be avoided as this is associated with increased risks of BPD and periventricular leucomalacia [88, 89]. The required tidal volume increases with advancing postnatal age especially in extremely low birth weight infants [90]. When satisfactory gas exchange is achieved and spontaneous respiratory drive is present weaning should be started immediately by first decreasing PIP (likely to be the most injurious to the lung).

Recommendations

(1) MV should be used to support babies with respiratory failure as this improves survival (A).
(2) Avoid hypocapnia as this is associated with increased risks of BPD and periventricular leucomalacia (B).
(3) Settings of MV should be adjusted frequently with the aim of maintaining optimum lung volume (C).
(4) Duration of MV should be minimised to reduce its injurious effect on lung (B).

Avoiding or Reducing Duration of Mechanical Ventilation

There are now clear links between MV through an endotracheal tube and subsequent development of BPD and neurodevelopmental sequelae [91]. Interventions designed to avoid or shorten MV include caffeine therapy, CPAP or nasal intermittent positive pressure ventilation (NIPPV) with or without surfactant, INSURE, permissive hypercapnia, and aggressive weaning with early extubation.

Caffeine Therapy

Methylxanthines have been used for a long time to treat apnoea of prematurity and to facilitate successful extubation from MV. Until recently only the short-term benefits were known. The Caffeine for Apnea of Prematurity (CAP) study addressed the issue of long-term effects of neonatal caffeine therapy [92]. In one of the largest ever perinatal trials, 2,006 preterm babies weighing <1,250 g were randomised to caffeine or placebo in the first 10 days of life, continuing until the clinician determined that therapy for apnoea would no longer be needed. The babies assigned to caffeine came off ventilation a week earlier than those assigned placebo, with a corresponding significant reduction in BPD (36 vs. 47%) [92]. There was a transient reduction in weight gain during therapy, however, follow-up at 18 months confirmed improved outcomes for caffeine-treated babies, with reduced combined outcome of death or neurodisability [odds ratio (OR) 0.77; 95% CI 0.64–0.93], reduced rates of cerebral palsy (OR 0.58; 95% CI 0.39–0.87) and cognitive delay (OR 0.81; 95% CI 0.66–0.99) [93]. Subgroup analysis from the CAP cohort suggests that babies who are on MV and have caffeine started earliest appear to derive the most benefit [94]. Caffeine should be part of routine care for very preterm babies with RDS to facilitate extubation [95].

Nasal Intermittent Positive Pressure Ventilation

NIPPV is another promising new therapy that helps to keep preterm babies off MV. There are now several trials showing reduced requirement for reintubation in the days following extubation when NIPPV is compared to CPAP [96]. NIPPV can be used as the primary mode of providing respiratory support with some evidence of improved respiratory outcome [97]. There is considerable heterogeneity in the methods employed to deliver NIPPV and to date no study has been sufficiently powered to show reduction in BPD. This will hopefully be addressed by the Canadian NIPPV trial which is currently underway.

Permissive Hypercapnia

Tolerating higher $PaCO_2$ levels during weaning has also been tried to facilitate earlier extubation. Although there are limited data from clinical trials to support this approach [98, 99], clinicians are tolerating moderate hypercapnia and respiratory acidosis in an effort to reduce duration of MV. A recently published observational study from Canada showed that implementation of a ventilation weaning protocol resulted in earlier first extubation and overall reduction in duration of MV [100]. This protocol suggested tolerating pH down to 7.22 over the first 5 days and down to 7.20 thereafter to enable babies to be weaned from respiratory support.

Aggressive Weaning and New Modes of Conventional Ventilation

Once stabilised on MV, babies with RDS should be aggressively weaned towards extubation provided it is clinically safe and they have acceptable blood gases [101]. Extubation may be successful from a mean airway pressure of 6–7 cm H_2O on conventional modes and from 8–9 cm H_2O of CDP on HFOV, even in the most immature babies. Keeping stable very preterm babies on low rate MV for longer periods does not improve the chance of successful extubation [102]. Extubation to nasal CPAP reduces the risk of re-intubation (RR 0.62; 95% CI 0.49–0.77; NNT 6) [79]. Patient-triggered, or synchronised ventilation can shorten the duration of MV during the weaning process in very immature babies, but there is no evidence of any long-term benefit in terms of survival or reduction in BPD [103]. Targeted tidal volume ventilation may be useful in avoiding injurious overdistension and reducing hypocapnia, and a meta-analysis of small trials of this intervention shows shorter duration of ventilation, reduced rate of pneumothorax and a trend towards reduced BPD [104].

Recommendations

(1) Caffeine should be used in babies with apnoea and to facilitate weaning from MV (A). Caffeine should be considered for all babies at high risk of needing ventilation, such as those <1,250 g birth weight, who are managed on CPAP or NIPPV (B).
(2) CPAP or NIPPV should be used preferentially to avoid or reduce the duration of MV through an endotracheal tube (B).
(3) When weaning from MV it is reasonable to tolerate a moderate degree of hypercapnia, provided the pH remains above 7.22 (D).
(4) Synchronised and targeted tidal volume modes of conventional ventilation with an aggressive weaning approach should be used to shorten duration of MV (B).

Prophylactic Treatment for Sepsis

Congenital pneumonia may mimic RDS and the commonest organism is group B Streptococcus (GBS), although *Escherichia coli* and other organisms may also be responsible. For this reason it is 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. In women who are known to be colonised with GBS the risk of early onset sepsis can be reduced by administration of intrapartum antibiotic prophylaxis (RR 0.17; 95% CI 0.04–0.74; NNT 25), although no effect on mortality has yet been demonstrated [105].

Fungal sepsis is an emerging problem in very preterm infants and it is associated with a higher mortality and poorer neurodevelopmental outcome than bacterial sepsis alone [106]. Signs of fungal infection are often subtle, and diagnosis is often delayed so many centres are developing protocols for antifungal prophylaxis. The reported incidence of invasive fungal infection varies widely, but can be as high as 13% of very low birth weight infants in a study from Italy [107], contrasting with just 2% of these babies from a population-based survey in the UK [108]. Prophylactic fluconazole and nystatin can reduce invasive fungal infection rates, however, no study has been sufficiently powered to look at long-term outcomes and there are concerns about widespread antifungal use leading to the emergence of resistance [109]. There are additional risk factors for fungal infection which have been used as selection criteria in some centres to define a high-risk group for prophylaxis and they too report favourable outcomes [110]. One suggested regimen is fluconazole 3 mg/kg body weight twice weekly for 6 weeks [111].

Recommendations

(1) Antibiotics should be started in babies with RDS until sepsis has been ruled out. A common regimen includes penicillin/ampicillin in combination with an aminoglycoside, however, individual units should develop local protocols for antibiotic use based on the profile of bacterial pathogens causing early onset sepsis (D).
(2) Units should develop protocols for antifungal prophylaxis in very preterm babies based on the local incidence and risk factors (D).

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, management of the ductus arteriosus and support of the circulation to maintain adequate blood pressure and tissue perfusion.

Temperature Control

Traditional methods used to maintain body temperature in term newborns are ineffective in immature babies, so use of additional warming techniques are recommended. Radiant warmers can be used for accessibility in the NICU, 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 [112]. In preterm babies in incubators the use of a servo-controlled skin temperature at 36°C decreases neonatal mortality [113].

Recommendation

(1) Body temperature should be maintained at 36.5–37.5°C at all times (C).

Fluid and Nutritional Management

The limited randomised trials available do not support the proposal that fixed fluid and electrolyte therapies influence outcome in RDS. However, in clinical practice a fixed early fluid intake regimen is usually supplemented with individualised management, considering the state of hydration, any recent weight change and electrolytes. Maximum weight loss does not correlate with severity of RDS or other morbidities in infants with birth weight of <1,000 g [114]. Modest restriction of fluid intake increases early weight loss but has a positive effect in terms of reducing persistent ductus arteriosus (PDA) and necrotising enterocolitis [115]. There is no evidence to support the use of diuretics in RDS [116]. Preterm babies should be nursed in incubators with high (dependent on gestational age and postnatal age) relative humidity (40–60%) to reduce insensible water loss. A postnatal weight loss of up to 15% during the first 5 days (2–4% per day) of life is normal. Birth weight should be regained at around 12 days.

Early nutrition is an important part of the overall care plan for babies with RDS. 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 [117–119]. Early randomised trials showed that parenteral nutrition improved survival by 40% in babies of 28–30 weeks' gestation with RDS and it is associated with a shorter hospital stay [120, 121]. Full nutrition requirements for glucose, amino acids and lipids can be safely commenced on the first day of life and progressively increased to 3.5 g/kg/day of amino acids and 2.5–3.0 g/kg/day lipids [122–126]. To maintain normoglycaemia and promote optimal growth, carbohydrate in the form of glucose should be given in the range of 6–18 g/kg/day. Dextrose 10% solution at 100 ml/kg delivers 10 g/kg of glucose. On its own this supplies 40 kcal/kg energy which is only just sufficient to maintain basal metabolic rate from the first day. Growth will require up to 110 kcal/kg energy in addition to protein [127]. Tolerance to intravenous lipids should be monitored as their use is associated with increased pulmonary vascular resistance and decreased oxygenation [128]. As early as possible, minimal enteral or 'trophic' feeding, using ≤20 ml/kg/day of breast milk, should be provided to enhance maturation and function of the gastrointestinal tract, to decrease intolerance and time to full enteral feeds, increase weight gain and shorten hospitalisation [129, 130]. A Cochrane Review shows no increase in the risk of necrotising enterocolitis with early trophic feeding [131]. Early aggressive feeding has been recommended by some [122, 126] to reduce weight deficit at time of hospital discharge [124].

Recommendations

(1) Most babies should be started on intravenous fluids of 70–80 ml/kg/day while being kept in a humidified incubator (D).
(2) Fluid and electrolyte therapy should be tailored individually in preterm infants, allowing a 2.5–4% daily weight loss (15% total) over the first 5 days (D).
(3) 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).
(4) Full parenteral nutrition can be initiated on day 1 (A). This may include starting protein at 3.5 g/kg/day and lipid at 3 g/kg/day in 10% dextrose solution.
(5) Minimal enteral feeding should be started from the first day (B). Early aggressive feeding is increasingly popular but level A evidence of its benefit is lacking.

Maintenance of Tissue Perfusion

Hypotension as well as low systemic blood flow are important factors determining poor tissue perfusion and can be related to brain injury [132]. There is a lack of data to determine what normal acceptable blood pressure values should be [133, 134], but many clinicians as a guide aim to maintain the mean arterial pressure above the gestational age in weeks. In the preterm newborn, blood pressure and systemic blood flow are not positively correlated especially during the transitional circulation in the first 3 days of life [135]. Poor tissue perfusion can be determined by clinical signs such as heart rate, capillary refill time and colour, although these are not always reliable. Other measures such as inadequate urine output and presence of significant metabolic acidosis are more valid, but these signs are often delayed. Bedside echocardiography and near infra red spectroscopy (NIRS) are now being used in some centres to determine mechanisms of low systemic blood flow and to evaluate poor cerebral tissue oxygenation more accurately [136]. Low systemic blood flow and hypotension during RDS may be related to hypovolaemia, large left-to-right ductus or atrial shunts, or to myocardial dysfunction. Knowing the cause can indicate the most appropriate choice of treatment. Volume expansion with 10–20 ml/kg normal saline, rather than colloid, can be considered as first-line treatment when hypovolaemia is confirmed or if the cause is not clearly established [137, 138]. Inhibitors of cyclooxygenase should be considered when there is poor perfusion and a large left-to-right shunt through the ductus is present. Dopamine is more effective than dobutamine to treat hypotension in preterm infants in terms of short-term outcome [139], 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 treatment of hypotension after conventional treatment has failed [140, 141]. More studies are needed to define tissue perfusion and find out how treatment of arterial hypotension influences the short- and long-term outcomes.

Recommendations

(1) Treatment of arterial hypotension is recommended when it is confirmed by evidence of poor tissue perfusion (C).
(2) Volume expansion with 10–20 ml/kg 0.9% saline should be used as first-line treatment of hypotension if myocardial dysfunction has been excluded (D).
(3) Dopamine (2–20 μg/kg/min) should be used if volume expansion fails to satisfactorily improve blood pressure (B).
(4) Dobutamine (5–20 μg/kg/min), as a first line, and epinephrine (0.01–1.0 μg/kg/min) as a second line, should be used if low systemic blood flow and myocardial dysfunction need to be treated (D).
(5) Hydrocortisone (1 mg/kg 8 hourly) should be used in cases of refractory hypotension where conventional therapy has failed (B).
(6) Echocardiographic examination may help to make decisions about when to start treatment for hypotension and what treatment to use (B).

Table 3. Summary of recommendations

Prenatal care	– Preterm babies at risk of RDS should be born in centres where appropriate care, including mechanical ventilation, is available. – If possible, birth should be delayed to allow the maximum benefit of antenatal steroid therapy.
Delivery room stabilisation	– Aim to delay cord clamping at birth. – Stabilise baby in a plastic bag under a radiant warmer to prevent heat loss. – Resuscitate 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. For more mature 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 if an individual baby will tolerate this. – For those who require mechanical ventilation, aim to ventilate for as short a time as possible, avoiding hyperoxia, hypocapnia and volutrauma. – Caffeine therapy should be used to minimise 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. – 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.

Management of Persistent Ductus Arteriosus

PDA may provide clinical problems for very preterm babies with RDS. Prophylactic indomethacin will reduce PDA and intraventricular haemorrhage, but there is no difference in long-term outcome [142]. Indomethacin or ibuprofen may be used to promote ductus closure when there are early signs of PDA such as hypotension (especially low diastolic blood pressure) with wide pulse pressures. The efficacy of indomethacin and ibuprofen are equivalent although ibuprofen is associated with a lower rate of renal adverse effects [143]. At present there is insufficient evidence of either short-term benefit or improved long-term outcomes when treating PDA with either indomethacin or ibuprofen or surgical ligation, although there is an observed association between surgical ligation and an increased risk of long-term adverse effects [144]. According to post-hoc analysis of a randomised trial, prophylactic ligation of PDA within 24 h of birth increases the risk of BPD [145].

Recommendations

(1) If a decision is made to attempt therapeutic closure of the PDA, then indomethacin or ibuprofen have been shown to be equally efficacious (B).
(2) Pharmacological or surgical treatment of presymptomatic or symptomatic PDA must be based on individual assessment of clinical signs and echocardiographic findings suggesting poor tolerance of PDA (D).

Miscellaneous

Some aspects of RDS management arise infrequently, but it is important to be aware of them. RDS can occur in babies born close to or at term, particularly if born by elective caesarean section before 39 weeks of gestation. RDS should be considered as a differential diagnosis in any baby with early respiratory distress, and surfactant therapy considered as part of the management [3, 146]. Some term babies with RDS may suffer from surfactant protein B or ABCA3 deficiency. These, especially the former, are extremely rare and these babies need specialised care which

is beyond the scope of this article. In term and near-term infants RDS may be associated with persistent pulmonary hypertension. These babies benefit from inhaled nitric oxide therapy [147]. This has also been administered to preterm babies in an attempt to reduce ventilation-perfusion mismatching and decrease pulmonary inflammation [48]. In contrast to term infants, several large randomised controlled studies of inhaled nitric oxide in preterm babies have failed to demonstrate clear benefits in terms of survival or reduced BPD [148]. Preterm babies with RDS occasionally develop massive pulmonary haemorrhage, particularly in the presence of a large PDA. Additional surfactant replacement therapy can be useful in this setting to counteract surfactant inhibition by blood and improve oxygenation, although there are no good randomised trials to support this [149]. Surfactant therapy has also been administered later in the course of respiratory disease, in babies with evolving BPD, and improvements in oxygenation occur but this effect is not sustained [59, 150].

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 management of preterm babies with RDS (A).
(3) Surfactant therapy can be used to improve oxygenation following pulmonary haemorrhage (C).
(4) Surfactant replacement for evolving BPD leads to only short-term benefits and cannot be recommended (C).

Finally, the recommendations discussed in detail on prenatal care, delivery room stabilisation, respiratory support and surfactant, and supportive care are summarised in table 3.

Conflicts of Interest

A European panel of experts was convened under the auspices of the European Association of Perinatal Medicine to develop evidence-based guidelines on the management of RDS. The meetings were supported by an unrestricted educational grant from Chiesi Farmaceutici, but none of the panel members received honoraria. The guidelines were prepared using evidence-based methodology as summarized in table 1. Henry Halliday and Christian Speer are consultants to Chiesi Farmaceutici and Ola Saugstad and Virgilio Carnielli are members of the Chiesi Farmaceutici Advisory Board.

Henry Halliday and Christian Speer are Joint Chief Editors of *Neonatology,* so editorial management and review of this article was kindly undertaken by a member of the Editorial Board, Eric Shinwell from Rehovot.

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