

International guidelines

European consensus guidelines on the management of neonatal respiratory distress syndrome*

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Abstract

Despite recent advances in the perinatal management of neonatal respiratory distress syndrome (RDS), controversies still exist. We report the recommendations of a Euro-

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pean panel of expert neonatologists who developed consensus guidelines after critical examination of the most up-to-date evidence in 2007. Strong evidence exists for the role of antenatal steroids in RDS prevention, but it is not clear if repeated courses are safe. 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 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 life saving but can cause lung injury, and protocols should be directed to avoiding mechanical ventilation where possible by using nasal continuous positive airways pressure. 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.

Keywords: Continuous positive airways pressure; evidence based practice; mechanical ventilation; oxygen supplementation; patent ductus arteriosus; respiratory distress syndrome; surfactant therapy; thermoregulation.

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 lack of alveolar surfactant along with structural immaturity of the lung and it is mainly confined to preterm babies. Clinically RDS presents with early respiratory distress comprising cyanosis, grunting, retraction, and tachypnea. 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 $\text{PaO}_2 < 50$ mm Hg (< 6.6 kPa) in room air, central cyanosis in room air or need for supplemental oxygen to maintain $\text{PaO}_2 > 50$ mm Hg (> 6.6 kPa) as well as classical chest X-ray appearances.

The aim of management of RDS is to provide interventions that will maximize the number of survivors 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 which have now been subjected to systematic reviews. This document reports the findings of a panel of experts from Europe who have developed consensus guidelines after critical examination of the most up-to-date evidence in early 2007.

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

Prenatal care

Treatment for RDS should begin before birth involving pediatricians as part of the perinatal team. Preterm babies at risk of RDS should be born in centers where appropriate skills are available for stabilization and ongoing respiratory support, including intubation and mechanical ventilation. There is often prior warning of impending preterm delivery, allowing time for interventions to be considered including *in utero* (maternal) transfer where appropriate. Preterm delivery can be delayed by using antibiotics in the case of preterm, pre-labor rupture of the membranes [55], and tocolytic drugs can be used in the short-term to delay birth [5, 57, 58, 77] to allow safe transfer to a perinatal center and to enable prenatal corticosteroids to take effect. These are given to mothers to reduce the risk of neonatal death [relative risk (RR) 0.69; 95% confidence interval (CI) 0.58–0.81; NNT 20] and the use of a single course of prenatal corticosteroids does not appear to be associated with any significant maternal or fetal adverse effects [80]. Betamethasone is the corticosteroid of choice to enhance fetal lung maturity because of an associated reduced risk of cystic periventricular leukomalacia when compared with dexamethasone [9, 51]. The recommended regimen is two doses of 12 mg given intramus-

cularly 24 h apart [80]. Prenatal corticosteroid therapy is recommended in all pregnancies with threatened preterm labor below 35 weeks' gestation. Although a statistically significant reduction in rates of RDS in babies <28 weeks has not been demonstrated in clinical trials of prenatal corticosteroids, this is probably because of inadequate numbers of very immature babies included in the original studies [80]. Improved neurological outcome has been demonstrated for even the tiniest babies [10, 80]. The optimal treatment to delivery interval is more than 24 h and <7 days after the start of steroid treatment [80].

There is continuing controversy over the use of repeated courses of prenatal corticosteroids. Although there may be clinical benefits of giving a second course in cases where delivery has not occurred in terms of further reducing RDS [25], long-term follow up data are not yet available. In animal studies there are changes in brain myelination following repeated exposure to prenatal steroids [47, 113] and in a large cohort study a decrease in newborn head circumference has also been observed with increasing prenatal steroid exposure [36]. The most recent Cochrane systematic review does not recommend routine repeat courses of prenatal steroids [24].

Recommendations

1. Clinicians should offer a single course of prenatal betamethasone to all women at risk of preterm delivery (before 35 weeks' gestation) including threatened preterm labor, antepartum hemorrhage, preterm rupture of membranes or any condition requiring elective preterm delivery because this treatment is associated with significant reductions in the rates of RDS, neonatal death, intraventricular hemorrhage and necrotizing enterocolitis (**A**).
2. Erythromycin 500 mg 6 hourly should be given to mothers with preterm pre-labor rupture of the membranes as this reduces the risk of preterm delivery (**A**).
3. In preterm labor it is reasonable not to use tocolytic drugs as there is no clear evidence that they improve outcome. However, clinicians should consider their short-term use to allow completion of a course of prenatal corticosteroids and/or *in utero* transfer to a perinatal center (**A**).
4. Although there may be a benefit in terms of reducing RDS from giving a second course of prenatal steroids in cases where a first course has been given and delivery has not taken place no other clinically important benefits have been identified and no firm recommendation can be made (**A**).

Delivery room stabilization

Babies with surfactant deficiency have difficulty achieving adequate functional residual capacity and maintain-

Table 1 Grades of recommendation and levels of evidence.

Grade of recommendation	Level of evidence
A	At least one high quality meta-analysis of randomized 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/

ing alveolar aeration. Traditionally many babies have been resuscitated with bag and mask ventilation, often using 100% oxygen [49], followed by early intubation for prophylactic surfactant administration, with subsequent manual ventilation with 100% oxygen. There is now evidence that resuscitation with 100% oxygen is associated with increased mortality in term and near-term newborn babies [84]. Pure oxygen may also be harmful to preterm infants [67, 106], 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 versus air [67]. In addition, it is also becoming clear that uncontrolled tidal volumes, either too large or too small, may also be detrimental to the immature lung [14, 50]. Delivery room continuous positive airways pressure (CPAP) has come into widespread use although it is not clear at present if this will reduce the need for subsequent surfactant treatment or mechanical ventilation [33, 41]. Pulse oximetry in the immediate newborn period provides useful information on heart rate during resuscitation and may help to avoid hyperoxic peaks [52]. During the transitional phase after birth, saturations should rise gradually from around 60 to 90% over 5 min [52]. Oximetry may identify babies outside of this range and help to guide inspired oxygen delivery. Clinical trial evidence from resuscitation of preterm babies is limited and therefore the recommendations are weak.

Recommendations

1. The lowest concentration of oxygen possible should be used during resuscitation, provided there is an adequate heart rate response ($>100/\text{min}$) as this reduces cerebral vasoconstriction (**B**) and may reduce mortality (**B**).
2. Start resuscitation with CPAP of at least 5–6 cm water via mask or nasal prongs to stabilize the airway and establish functional residual volume (**D**).
3. If positive pressure ventilation is needed for resuscitation, aim to avoid excessive tidal volumes by incorporating resuscitation devices which measure or limit the peak inspiratory pressure as this might reduce the risk of lung injury (**D**).
4. Intubation should be reserved for babies who have not responded to positive pressure ventilation by mask or those requiring surfactant therapy (**D**).
5. Pulse oximetry may be used to guide oxygen delivery during resuscitation, aiming to avoid hyperoxic peaks. It must be remembered that normal saturations during transition after birth may be between 50–80% (**D**).

Surfactant therapy

Surfactant therapy has revolutionized neonatal respiratory care over the past two decades. Most aspects of its

use have been tested in multicenter randomized controlled trials, many of which have been subjected to meta-analyses. It is clear that surfactant therapy, whether given prophylactically [96], or as rescue therapy [97] to babies with or at risk of developing RDS reduces the risk of pneumothorax (pulmonary air leaks) and neonatal death. The trials have focused on determining the optimal dose, timing of dosing, the best method of administration and the best surfactant preparation.

Surfactant dosing and re-dosing

An experienced neonatal resuscitation/stabilization team is essential for surfactant administration. At least 100 mg/kg of phospholipid is required [112] but there is some evidence that 200 mg/kg may be better for treating established RDS [78]. Most clinical trials have used either bolus instillation or fairly rapid instillation over one minute and this appears to result in better distribution of surfactant [108]. Administration via a dual lumen endotracheal tube without disconnection from mechanical ventilation is also effective at reducing short-term side effects such as hypoxemia and bradycardia [108]. Surfactant therapy clearly works better the earlier in the course of RDS it is given [99]. 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 therapy unnecessarily [99]. These trials were carried out in an era of low prenatal corticosteroid use and for this reason a lower gestation below which prophylactic surfactant can be recommended as a routine may be appropriate, perhaps <27 weeks. Attempts to predict the development of RDS in individual babies using the stable microbubble test may reduce unnecessary intubations, but this practice has not yet come into widespread use [34]. 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 is made. In babies who require surfactant, mechanical ventilation can also be avoided by the "INSURE" technique (intubate – surfactant – extubate to CPAP) and this method has been shown in randomized trials to reduce the need for mechanical ventilation [102]. The earlier in the course of RDS that surfactant is given the greater the chance of avoiding ventilation [111].

Following surfactant administration there may, after a variable period of time, be a need for a further dose of surfactant. In randomized trials it would appear that two doses are better than a single dose [95] and a study with poractant alfa (see below) showed that up to three doses compared to a single dose reduced mortality (13% vs. 21%) and pulmonary air leaks (9% vs. 18%) [100]. There are two approaches to repeat dosing, the first being rigid with further doses of surfactant being administered after a set time period and the second being more flexible,

with repeat dosing occurring at the pediatricians' discretion. The latter is the more common approach. One study suggests that repeat surfactant may be given with a high threshold and this reduces the need for re-treatment without adversely affecting outcome [53], and there are pharmacokinetic data to support this approach [112]. Surfactant therapy beyond the first week of life results in acute responses only with no evidence of any difference in long-term outcome [76].

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 (see Table 2). Studies have compared colfosceril palmitate with calfactant and beractant, and pumactant with poractant alfa. Natural surfactants are better than synthetic preparations with a meta-analysis of randomized controlled trials showing both a significant reduction in pulmonary air leak (RR 0.63; 95% CI 0.53–0.75; NNT 25) and reduced mortality (RR 0.86; 95% CI 0.76–0.98; NNT 50) [98]. Natural surfactants are therefore the treatment of choice. Trials comparing the natural bovine surfactants calfactant and beractant showed no difference in outcome when given prophylactically or as rescue therapy [15, 16]. 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 and a trend towards reduced mortality in each trial [78, 101]. Overall there may be a survival advantage (RR 0.29; 95% CI 0.10–0.79; NNT 14) with poractant alfa when a 200 mg/kg dose is compared with 100 mg/kg of beractant to treat established RDS [42]. Comparisons have been made between the new synthetic surfactant, lucinactant and colfosceril palmitate and beractant [72], and lucinactant

and poractant alfa [92]. This surfactant is not yet licensed to treat RDS in the newborn.

Recommendations

1. Babies with or at high risk of RDS should be given surfactant as this reduces mortality and pulmonary air leak (**A**).
2. Prophylaxis (within 15 min of birth) should be given to almost all babies under 27 weeks' gestation. Prophylaxis should be considered for babies over 26 weeks but <30 weeks' gestation if intubation is required in the delivery suite or if the mother has not received prenatal corticosteroids (**A**).
3. Early rescue surfactant should be given to untreated babies if there is evidence of RDS such as increasing requirement for oxygen (**A**). Individual units need to develop protocols for when to intervene as RDS progresses (**D**).
4. 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 mechanical ventilation or if over 50% oxygen is needed on CPAP at 6 cm H₂O as this reduces pneumothorax and probably also mortality (**A**).
5. For babies on CPAP a second dose of surfactant should be given if they are determined to need mechanical ventilation (**D**).
6. Natural surfactants should be used in preference to synthetic as they reduce pulmonary air leaks and mortality (**A**). Of the natural surfactants the bovine products beractant and calfactant seem similar in their efficacy but poractant alfa in a dose of 200 mg/kg for rescue therapy leads to improved survival compared to beractant (**B**).
7. Where possible, duration of mechanical ventilation should be shortened by immediate (or early) extu-

Table 2 Surfactant preparations 2007.

Generic name	Trade name	Source	Producer	Dose (volume)
Pumactant	ALEC [®]	Synthetic	Britannia (UK)	No longer manufactured
Bovactant	Alveofact [®]	Bovine	Lyomark (Germany)	50 mg/kg/dose (1.2 mL/kg)
BLES	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	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	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)

*Not available in Europe.

bation to CPAP following surfactant administration provided the baby is otherwise stable (**B**).

Oxygen supplementation beyond stabilization

There is currently no firm evidence to guide optimal oxygen saturation targeting during the acute management of RDS. Studies in more mature babies requiring resuscitation suggest that recovery is quicker when using air compared with 100% oxygen [82] with less evidence of oxidative stress [110] and no difference in long-term outcome [106]. Beyond the neonatal period data suggest that oxygen saturation targets in preterm babies receiving supplemental oxygen should be maintained below 93% and not exceed 95% in order to prevent retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD) [6, 84]. 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 [64, 105]. 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 their course. There are also data to suggest that fluctuations in oxygen saturation can also be harmful being associated with an increased incidence of ROP [20, 26]. After using natural surfactant a hyperoxic peak may occur and this is associated with an increase in grades I and II intraventricular hemorrhage [21].

Antioxidants such as vitamins A and E and the enzyme superoxide dismutase have been administered to babies at risk of developing BPD in an attempt to reduce oxygen-free radical-induced lung inflammation. So far only vitamin A has shown promise, with a modest but statistically significant reduction in BPD in babies treated with intramuscular vitamin A compared with controls [27].

Recommendations

1. In babies receiving oxygen, saturation should be maintained at all times below 95% as this may reduce ROP and BPD (**D**).
2. After giving surfactant, avoid a hyperoxic peak by rapid reduction in FiO_2 as this is associated with grade I and II IVH (**C**).
3. Consider giving intramuscular vitamin A as this reduces BPD although it requires thrice weekly intramuscular injections for 4 weeks (**A**).

The role of CPAP in the management of RDS

Continuous positive airways pressure (CPAP) is often used as a substitute for mechanical ventilation to provide

respiratory support for babies with RDS, despite the lack of data from recent randomized trials to show its effectiveness in this population [104]. Mechanical ventilation is harmful to immature lungs and should be avoided if possible. CPAP reduces the need for re-intubation if applied following extubation from mechanical ventilation and at least 5 cm water pressure appears to be needed to achieve this [28]. There is no good evidence that use of CPAP will prevent surfactant deficiency but babies with mild RDS are often managed on CPAP without receiving surfactant treatment [81]. The earlier CPAP is applied, the greater the chance of avoiding mechanical ventilation (RR 0.55; 95% CI 0.32–0.96; NNT 6) [46]. There is no evidence to date of any differences in long-term outcomes among the various devices used to provide nasal CPAP [63], however, studies have shown that short binasal prongs are better than a single prong at reducing the need for re-intubation (RR 0.59; CI 0.41–0.85; NNT 5) [29]. Recently, devices such as the infant flow driver have been developed with the technology to provide a background of synchronized nasal ventilation. Small trials in babies with apnea have been promising with reduced extubation failure rates in babies on nasal back-up breaths [62]. Small studies in babies with RDS have shown decreased work of breathing on nasal ventilation compared with CPAP alone [3] but no long-term follow up data are available and larger studies are needed.

Recommendations

1. CPAP should be initiated in all babies at risk of RDS, such as those <30 weeks' gestation who are not receiving mechanical ventilation, until their clinical status can be assessed (**D**).
2. The use of CPAP with early rescue surfactant should be considered in babies with RDS in order to reduce the need for mechanical ventilation (**A**).
3. Short binasal prongs, such as those in the flow driver system, should be used rather than a single prong as they reduce the need for intubation (**C**) and a pressure of at least 6 cm water should be applied as this reduces the need for re-intubation in babies recently extubated (**A**).

Mechanical ventilation strategies

The aim of mechanical ventilation (MV) is to provide acceptable blood gases with minimum risks of lung injury, hemodynamic impairment and other adverse events such as hypocapnia associated with neurological impairment. Before surfactant became available MV was shown to reduce death from RDS [44]. MV can be provided as intermittent positive pressure ventilation (IPPV) or high frequency oscillatory ventilation (HFOV) [45]. The principle of MV is to stabilize the lung after recruitment to opti-

mal lung volume with adequate positive end-expiratory pressure (PEEP) or continuing distending pressure (CDP) on HFOV to keep the lung open during the whole respiratory cycle. Treatment of RDS with MV can be divided into four phases: recruitment, stabilization, recovery and weaning. For recruitment PEEP and peak inspiratory pressure (PIP), or CDP on HFOV are crucial. The stabilization should be achieved on the more compliant expiratory limb of the lung pressure-volume hysteresis curve. Once stabilized on MV, babies with RDS should be aggressively weaned towards extubation provided it is clinically safe and they have acceptable blood gases. Hypocapnia should be avoided wherever possible as this is associated with increased risks of BPD and periventricular leukomalacia [30, 39]. Extubation may be successful from 6–7 cm H₂O of mean airway pressure on conventional modes and from 8–9 cm H₂O of CDP on HFOV, even in tiny babies. Extubation to nasal CPAP reduces the risk of re-intubation (RR 0.62; 95% CI 0.49–0.77; NNT 6) [28].

All types of MV are potentially injurious to the lung. A strategy for minimizing lung injury is to optimize lung volume whilst avoiding excessive tidal volumes and atelectasis. Previously it was believed that this could best be achieved with HFOV, however, with the introduction of lung protective, low tidal volume conventional ventilation some of the benefits of HFOV over conventional ventilation as regards lowering the incidence of BPD have been attenuated [17]. Strategy and technique are more important than mode of ventilation and the method that is most successful in your own unit should be employed [7, 23, 30]. HFOV may be useful as a rescue therapy in babies with severe respiratory failure on IPPV [37]. Rescue HFOV reduces new pulmonary air leaks (RR 0.73; 95% CI 0.55–0.96; NNT 6) but there are still concerns about increased risks of intraventricular hemorrhage (RR 1.77; 95% CI 1.06–2.96; NNH 6) in preterm babies [13]. The effect of surfactant is to improve compliance and therefore lung volumes. Over-distension should be considered if a baby is deteriorating on MV following surfactant administration. 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.

Many newer types of MV are now available, incorporating flow sensors that can accurately detect breathing efforts and measure inspiratory and expiratory gas volumes. Most of these newer ventilator modes have been studied in small trials. Targeted tidal volume ventilation may be useful in avoiding injurious over-distension and reduce hypocapnia episodes, but there are no long-term follow-up data as yet to support its routine use [56, 70]. Patient triggered, or synchronized ventilation can shorten the duration of MV during the weaning process in very tiny babies, however, there is no evidence of any long-term benefit in terms of survival or reduction in BPD [38]. Tolerating higher PaCO₂ levels during weaning has also

been attempted to facilitate earlier extubation, although there are insufficient data to date to support this approach [114]. Caffeine therapy may facilitate successful extubation and reduce BPD, however, long-term follow up data are needed to determine the safety of this therapy [86]. Inhaled nitric oxide has also been administered to preterm babies in an attempt to reduce ventilation-perfusion mismatching and decrease pulmonary inflammation, but there is no clear evidence to date that this leads to improved outcomes or a reduced risk of BPD [8, 59, 109].

Recommendations

1. Mechanical ventilation (MV) should be used to support babies with respiratory failure as this improves survival (**A**).
2. All modes of MV can induce lung injury and should be limited to the shortest possible duration provided there is a reasonable chance of successful extubation (**D**).
3. Avoid hypocapnia, wherever possible, as this is associated with increased risks of BPD and periventricular leukomalacia (**B**).
4. Following extubation, babies should be put on nasal CPAP as this reduces the need for re-intubation (**A**).

Prophylactic treatment for sepsis

Early-onset group B streptococcal (GBS) disease is the most frequent cause of serious infection in the newborn period [18]. In women who are known to be colonized with GBS the risk of early onset sepsis can be reduced by administration of intrapartum antibiotic prophylaxis (RR 0.12; 95% CI 0.03–0.44; NNT 20) [93]. Early onset GBS sepsis is relatively rare, affecting up to 1:1000 births, however, in preterm babies up to 30% of cases will die and there is a high proportion of adverse neurological sequelae in survivors, particularly those with meningitis. Prematurity, amongst other risk factors, increases the likelihood that GBS is present and the symptoms of early onset GBS pneumonia closely mimic RDS. 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, thrombocytopenia or an elevated C-reactive protein. Treatment with antibiotics against GBS should be initiated in all babies with RDS until sepsis has been excluded, usually by a negative blood culture after 48 h.

Recommendation

1. Babies with RDS should routinely have blood cultures performed before starting treatment with intravenous penicillin or ampicillin (**D**). This may reduce

death from early onset GBS although data to support this approach are not available from randomized controlled trials.

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.

Temperature control

Traditional methods used to maintain body temperature in term newborns are ineffective in immature babies [22], so use of additional warming techniques are recommended. Immediately after birth all efforts should be made to reduce heat loss to prevent hypothermia since this improves survival [89]. Hypothermia can be prevented by wrapping and drying the baby with pre-warmed blankets, removing wet blankets, keeping the baby away from cold sources and by the use of servo-controlled radiant warmers [1]. Use of a polyethylene bag or wrap will reduce hypothermia during care in the delivery room and transfer to the NICU in infants <28 weeks and it might reduce hospital death rate, although it is not clear what the risks of hyperthermia are with this technique and there are no long-term follow up studies [69]. 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 [35]. In preterm babies in incubators the use of a servo-controlled temperature at 36°C decreases neonatal mortality [91].

Recommendations

1. Axillary temperature should be maintained at 36.1–37°C and abdominal skin temperature at 36–36.5°C [4] (C).

Fluid and nutritional management

Current evidence from randomized controlled trials is insufficient to conclude that fluid and electrolyte therapy plays a major role in the pathogenesis of RDS and BPD [65]. Extracellular water and sodium contraction during the first postnatal days is likely to be physiological and daily weighing is useful to help guide fluid management. There is little evidence that restriction of fluid intake has a positive effect although increasing fluid intake may be deleterious with increased incidence of persistent ductus

arteriosus (PDA), BPD and necrotizing enterocolitis (NEC) [11]. Most babies should be started on intravenous fluids of 70–80 mL/kg/day [87]. Sodium intake should initially be restricted, then initiated after the onset of diuresis [43]. There is no evidence to support the use of diuretics in RDS [19].

Early nutrition is an important part of the overall care plan for babies with RDS. Initially, enteral feeding might not be possible or desirable, so nutrients should be given as parenteral nutrition (PN) to provide enough energy and amino acids to prevent a negative balance and to promote early growth by increasing protein synthesis and nitrogen retention [2, 79, 90]. Traditionally, nutrients are introduced slowly but a recent study has shown that full nutrition requirements for glucose, amino acids and lipids can be safely provided to preterm infants from the first hour after birth [48]. Early randomized trials showed that PN improved survival by 40% in babies of 28–30 weeks' gestation with RDS and it is associated with a shorter hospital stay [40, 68]. Whether or not enteral feeding is safe when there are hemodynamic upsets such as hypotension, PDA and indomethacin therapy is unknown but RDS itself is not a contraindication to feeding and small volumes of breast milk may be given to babies provided they are clinically stable, even if there is an umbilical catheter *in situ* [54]. As early as possible, minimal enteral or "trophic" feeding using 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 hospitalization [12, 66, 71]. A Cochrane review shows no statistically significant increase in the risk of NEC with trophic feeding [107].

Recommendations

1. Most babies should be started on intravenous fluids of 70–80 mL/kg/day while being kept in >80% ambient moisture in the incubator (D).
2. Fluid and electrolyte therapy should be tailored individually in preterm infants, allowing a 2.5–4% daily weight loss (15% total), rather than imposing a fixed daily progression (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. There should be early introduction of protein, calories and lipids in PN as this improves survival (A).
5. Minimal enteral feeding should be started in stable babies with RDS as this will shorten duration of hospitalization (B).

Maintenance of blood pressure

Arterial hypotension has been associated with increased morbidity and mortality in preterm infants. However, there

is little evidence that the treatment of arterial hypotension improves clinical outcome. There is a lack of data to determine what normal acceptable blood pressure values should be [32, 88] but many clinicians as a guide aim to maintain the mean arterial pressure above the gestational age in weeks. In the preterm newborn, systemic blood pressure and cardiac output are not closely correlated [60], and it is cardiac output and tissue perfusion that are probably the most important determinants of outcome. Cardiac output is technically difficult to measure ultrasonographically because of the presence of ductal shunts. To an extent normal tissue perfusion can be determined clinically by adequate urine output and absence of significant metabolic acidosis.

Hypotension during the acute phase of RDS is only rarely related to hypovolemia, and volume expansion should be limited to 10–20 mL/kg [75]. Administration of colloids is associated with increased mortality and oxygen dependency and crystalloids should be used in preference when hypovolemia is suspected [94]. Dopamine is better than dobutamine to treat hypotension in preterm infants in terms of short-term outcome [103], but dobutamine may be a more rational choice if the cause of hypotension is myocardial failure. Hydrocortisone may be used for treatment of hypotension after conventional treatment has failed [73] but there may be an increased risk of intestinal perforation especially if indomethacin has been used concomitantly.

Recommendations

1. Treatment of arterial hypotension is recommended when it is accompanied by evidence of poor tissue perfusion (**C**).
2. Doppler-ultrasound assessment of systemic hemodynamics should be used when possible to determine the mechanisms responsible for hypotension and to guide treatment (**D**).
3. In the absence of cardiac ultrasound, volume expansion with 10 mL/kg 0.9% saline should be used as first line treatment of hypotension to exclude hypovolemia (**D**).
4. Dopamine (2–20 μ g/kg/min) rather than dobutamine should be used if volume expansion fails to satisfactorily improve blood pressure (**B**).
5. Dobutamine (5–10 μ g/kg/min) or epinephrine (0.01–1 μ g/kg/min) infusions may be used in addition, if maximum dose dopamine fails to satisfactorily improve blood pressure (**D**).
6. Hydrocortisone (1 mg/kg 8 hourly) should be used in cases of refractory hypotension where conventional therapy has failed (**B**).

Management of persistent ductus arteriosus

Persistent ductus arteriosus (PDA) may provide clinical problems for very preterm babies with RDS. Prophylactic

indomethacin will reduce PDA and IVH but there is no difference in long-term outcome [61, 85]. Alternatively, indomethacin or ibuprofen may be used when there are early signs of PDA such as hypotension with wide pulse pressures. The efficacy of indomethacin and ibuprofen for treatment of established PDA is equivalent although ibuprofen is associated with a lower rate of renal adverse effects [74]. 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. 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.

Recommendations

1. Indomethacin prophylaxis reduces PDA and severe IVH but there is no evidence of differences in long-term outcome, therefore firm recommendations cannot be made (**A**).
2. If a decision is made to attempt therapeutic closure of the PDA then indomethacin or ibuprofen have been shown to be equally efficacious (**B**).

Summary of recommendations

Preterm babies at risk of RDS should be born in centers where appropriate care, including mechanical ventilation, is available. If possible, birth should be delayed to allow the maximum benefit of prenatal corticosteroid therapy. At birth, resuscitate gently, avoiding excessive tidal volumes and exposure to 100% O₂ if possible, provided there is an adequate heart rate response (> 100/min). For extremely preterm infants, consider intubation in delivery suite for prophylactic surfactant administration. For more mature babies, CPAP should be initiated early, and early rescue surfactant administered if signs of RDS develop. Natural surfactants should be used and given as early as possible in the course of RDS. More mature babies can often be extubated to CPAP immediately following surfactant, and a judgment 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, aiming to avoid hyperoxia and hypocapnia. Repeat doses of surfactant may be required if there is ongoing evidence of RDS. Following extubation, babies should be maintained on CPAP until it is clear that they are stable.

Whilst managing RDS good supportive care is also essential. Antibiotics should be initiated until sepsis has been ruled out. Body temperature should be maintained in the normal range at all times and careful fluid balance with nutritional support, initially in the form of parenteral nutrition, should be instigated. Blood pressure should be

monitored regularly, aiming to maintain normal tissue perfusion, if necessary using inotropes and consideration should be given to whether pharmacological closure of the ductus arteriosus is indicated.

Conflict of interest

A European panel of experts was convened by Chiesi Farmaceutici, Parma, Italy to develop evidence based guidelines on the management of RDS. The process was supported by an educational grant and members of the panel received honoraria for their contributions. The guidelines were prepared using evidence based methodology as summarized in Table 1 and the pharmaceutical company had no editorial input. Ola Didrik Saugstad is a member of Chiesi Farmaceutici Advisory Board.

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