

Guidelines for good practice in the management of neonatal respiratory distress syndrome.

**Report of the second working group of the British Association of Perinatal Medicine.
Guideline produced in November 1998, Not valid beyond 2002**

Aims of the working group

A joint Working Group of the Research Unit of the Royal College of Physicians and the British Association of Perinatal Medicine devised the first BAPM RDS guidelines, meeting in November 1990. The guidelines were published in the Archives of Disease in Childhood (1) and were widely circulated. Comments suggested that the guidelines were found to be useful, and clinicians used them to develop their own protocols.

Guidelines can never replace clinical judgement, and local needs may dictate differences in priority or approach. In view of the enthusiastic response to the first guidelines and the publication of new clinical trials in many areas relevant to neonatal RDS the second Working Party was convened, and met on the 19th February 1998. Members are listed at the end of the paper. The group prepared referenced background papers, met to set priorities, and then circulated drafts of this document until a consensus was reached. Consultation and suggestions were sought from the whole BAPM membership in September 1998. Suggestions were gratefully accepted from several individuals whose names are listed in the appendix. This final version represents the work of many individuals.

Definition of respiratory distress syndrome

Neonatal respiratory distress syndrome (RDS) is a condition of increasing respiratory distress, commencing at, or shortly after, birth and increasing in severity until progressive resolution occurs among the survivors, usually between the 2nd to 4th day. It is due, at least in part, to insufficiency of pulmonary surfactant and is mainly confined to preterm infants. RDS is manifest by respiratory distress (cyanosis, tachypnoea, grunting, and recession) and respiratory failure is diagnosed by blood gas analysis. Oedema is frequently seen on the second day due to fluid retention and capillary leak. The diagnosis can be confirmed by an X ray film showing ground glass appearance and air bronchograms, although these radiological features are not pathognomic of RDS.

Presentation and implementation of the new guidelines

The format of the guideline follows that recommended by the NHS executive and the RCPCH wherever possible (2). Statements of good practice are supported by references to randomised controlled clinical trials of good design where these exist. These recommendations constitute “grade A” recommendations and can be recognised by boxing and shading of the text. Other recommendations are based on published clinical studies but not randomised controlled trials, and these are offered as grade B recommendations. In some instances the working group agreed that a course of action was appropriate, even if there was no published evidence to support it. These statements are followed by a (C) to indicate both consensus and grade C evidence. Where sound evidence does not exist, best clinical practice is to enrol patients into a randomised controlled trial, and where these are known to be ongoing (via the Clinical Trials Group of the BAPM) they have been mentioned. There are still many areas where no evidence exists and no trials are planned, and further work is needed. These guidelines are intended to assist doctors and nurses who are caring for babies with RDS to manage cases and to audit their own practice against a nationally agreed standard. They are not intended to replace a doctor's clinical judgement, and do not represent the only way in which RDS can be managed. They do, however, provide a framework within which audit and review of clinical practice can take place.

Prenatal management

The vast majority of babies who develop RDS do so because they are born preterm. Babies born at less than 32 weeks gestation are the most likely to require artificial ventilation for RDS. More than a half of babies born at less than 30 weeks develop the condition, and about 32% do so at 32 weeks (3). Babies of less than 26 weeks gestation, at the margin of viability, present special problems and a specific BAPM guideline on this topic is in preparation. Other guidelines for the management of the ethical dilemmas raised by this very preterm group have been published by FIGO (4) and the Canadian Society of Obstetricians (5).

There is often prior warning of impending preterm delivery, allowing time for several antenatal interventions to be considered including in-utero transfer. These form an important aspect of the management of RDS.

Prevention of Preterm Delivery

Research in this important area continues, and was thoroughly reviewed by Goldenberg (6). Maternal smoking, Mullerian duct abnormalities, and working during pregnancy all increase the risk of preterm birth. Routine iron supplementation prevents maternal anaemia and one trial showed a statistically nonsignificant reduction in preterm birth when routine iron administration was used. Zinc, magnesium and fish oil supplementation of the diet have all been suggested, but the evidence is not strong. The main benefits have been seen in the area of infection detection. Fibronectin can be detected in about 10% of high vaginal swabs

taken at 24-27 weeks of pregnancy. Fetal fibronectin has been linked to preterm labour, and an ongoing study is examining whether any benefit can be obtained from metronidazole therapy when a positive maternal swab result is found.

Cervical cerclage

Women who have had three or more second trimester miscarriages and/or preterm deliveries without obvious reason can benefit from prophylactic cervical cerclage early in pregnancy (7). In the presence of cervical dilatation with intact membranes and without evidence of infection emergency cervical cerclage should be considered, and has been shown to prolong pregnancy (B) (8). New research is examining the value of ultrasound estimation of cervical length as a predictor of preterm delivery and prophylactic cervical cerclage may be offered to this group as part of a randomised trial. This treatment is experimental at the time of writing, and should only be offered in the context of a properly conducted randomised controlled trial (C).

Antibiotics

Asymptomatic bacteriuria

Meta-analysis of 12 well controlled clinical trials indicated that antibiotic treatment of asymptomatic bacteriuria reduces the risk of preterm delivery by about 40% (9). There is no specific benefit against RDS. Routine screening for asymptomatic bacteriuria at an early stage in pregnancy can be worthwhile in populations where the risk is high (B) (10).

Antibiotics in preterm labour

Bacterial vaginosis is emerging as a clear risk factor for preterm delivery (11). Treating women presenting in preterm labour with antibiotics has, in some studies, been shown to be of benefit (B). However, in other trials the effect was limited to women with a previous preterm birth who had *Gardnerella vaginalis* treated with metronidazole and erythromycin (12,13). The ORACLE trial is currently evaluating the role of amoxicillin/clavunalic acid (Augmentin) and erythromycin in idiopathic preterm labour or preterm prelabour membrane rupture, and over 5,400 women have been recruited. In the meanwhile the role of antibiotics in women with preterm labour with intact membranes but without bacterial vaginosis is not clear (C).

Antibiotics in preterm prelabour rupture of membranes (PPROM)

Meta-analyses of trials of antibiotics for preterm prelabour rupture of membranes showed that treatment was associated with a reduction in the incidence of preterm delivery, and a reduction in neonatal infections and periventricular haemorrhage but had no effect on perinatal mortality, with conflicting evidence about the incidence of RDS (14,15). The benefits of antibiotic treatment for preterm prelabour rupture of membranes outweigh the potential harm and treatment with erythromycin 500mg qds plus amoxicillin/clavunalic acid (Augmentin) 375 mg qds for 7 days is currently recommended (A). An alternative regimen if there is concern about *Mycoplasma hominis* is clindamycin 150 mg qds for 7 days.

Intrapartum antibiotic prophylaxis for mothers who are carriers of group B streptococcus

Intrapartum penicillin has been shown to interrupt the vertical transmission of group B streptococcus to the infant and to prevent neonatal death from the early onset septicaemia caused by this organism (A). There can be no doubt about the effectiveness of selective intrapartum prophylaxis, which has been confirmed by a meta-analysis which showed a 30 fold reduction in GBS disease (16). More than a decade has passed since the first clinical trial that demonstrated the effectiveness of intrapartum antibiotic prophylaxis (17), but still prevention strategies have not been implemented widely or consistently, and the incidence of neonatal GBS disease has not declined. Two alternative strategies exist. In the first strategy, intrapartum antibiotic prophylaxis is offered to women identified as GBS carriers through prenatal screening cultures collected at 35–37 weeks' gestation and to women who develop premature onset of labour. In the second strategy, intrapartum antibiotic prophylaxis is provided to women who develop one or more risk conditions during labour. Screening is not done. Risk factors include prolonged membrane rupture for more than 18 hours; maternal pyrexia of more than 38°C on two occasions more than 2 hours apart; prematurity; and GBS disease in a previous child. No clinical trials have compared the efficacy of the two strategies, and both strategies are in use in different parts of the world. Individual hospitals should develop a strategy suitable for the local population according to the known level of maternal colonisation with this organism (B).

Tocolytics

The risk/benefit equation relating to B-mimetic treatment in preterm labour has been extensively debated over the last 20 years, and ritodrine became particularly contentious following the results of a trial by the Canadian Preterm Labor Investigators Group (18). Kierse has incorporated these results into a meta-analysis for the Cochrane Collaboration, which is now based on over 1600 cases (19). The results show that ritodrine treatment delays delivery by more than 24 hours but that this delay is not associated with a reduction in RDS or perinatal death. Ritodrine use should be limited to the short term to allow time to prepare for a preterm delivery and for a full course of antenatal steroids to be administered. In view of the rare but serious side effect of pulmonary oedema, ritodrine is contraindicated in women with cardiac disease, hyperthyroidism, or diabetes (C). In these women indomethacin is the tocolytic of choice (C) (20).

Prenatal amelioration of severity of RDS

Corticosteroids

Overview of the results of 18 trials enrolling over 3,700 babies provide clear evidence that prenatal corticosteroids reduce the risk of RDS with a typical odds ratio for RDS of 0.35 (95% confidence intervals 0.26-0.45) (21). The greatest benefit against RDS is seen when the time interval between the start of treatment and delivery is more than 48 hours and less than seven days (A). There is no effect on the incidence of chronic lung disease, but the reduction in incidence of intracranial hemorrhage appears to be translated into a reduction of cerebral palsy in the survivors (B). The effect is seen over a wide range of

gestational ages and is independent of race and gender (A).

All women between 23 and 34 completed weeks of gestation considered to be at risk of delivery within 7 days are candidates for antenatal steroid administration (A). Therapy should be initiated even when delivery is anticipated within a few hours. The RCOG guideline (22) recommends treatment at up to 36 completed weeks of gestation, but if the upper limit of 36 weeks is used it should be remembered that steroids may be inappropriate for women with PPROM at 34-36 weeks gestation (C). The cost-effectiveness of antenatal steroid therapy is less at 34-36 weeks gestation; it has been estimated that 94 women delivering at 34-37 weeks would need to be treated to prevent one case of RDS compared to only 5 before 31 weeks (23). The most extensively studied regimen is 12 mg of betamethasone intramuscularly repeated after 24 hours, but any regimen which delivers a total dose of 24 mg betamethasone within a period of 24-48 hours is acceptable. Treatment should not be repeated within 7 days. After 7 days the treatment should only be repeated after careful consideration because the risks and benefits of repeated courses of antenatal steroids are still unknown (C). A multicentre study is in progress evaluating the effects of multiple courses of steroids versus a single course.

There are very few circumstances in which steroid treatment should be withheld. Many obstetric units are achieving rates of antenatal steroid administration which are in excess of 80% in women delivering at less than 35 weeks. Contraindications to antenatal corticosteroids are maternal thyrotoxicosis, cardiomyopathy, active maternal infection or chorioamnionitis (C). Maternal diabetes, pre-eclampsia, preterm prelabour rupture of the membranes or treated suspected chorioamnionitis need not be regarded as contra-indications to steroids (C).

TRH

Experiments in preterm lambs suggested synergism between TRH and glucocorticoids, and clinical trials followed. Crowther's most recent meta-analysis for the Cochrane Pregnancy and Childbirth database included the large ACTOBAT study and 6 other trials (24,25). These trials evaluated the addition of TRH to antenatal corticosteroid therapy in women at risk of preterm delivery. There was no evidence for a reduction in the risk of RDS or mortality (A). The existing trials used 200 micrograms of TRH. Several further large trials are in progress using a dose of 400 micrograms. The BAPM Working group endorsed the conclusions of the NIH consensus panel and the RCOG Guideline, that the use of TRH remains experimental and cannot be recommended except in the context of further RCTs (22,26).

Mode of delivery

Delivery by caesarean section is associated with a higher risk of RDS than vaginal delivery at term (B)(27). There are insufficient data on which to base a conclusion at preterm gestations although one national study suggested a reduction in handicap rate at five years after caesarean section delivery (28). Grant has conducted a meta-analysis of the 5 existing trials which assessed elective versus selective caesarean section for women in preterm labour. His conclusion was that there is insufficient evidence to justify caesarean

section delivery for preterm infants whether or not the fetus is presenting by the breech (B). The results showed a reduction in cord prolapse and intubation at delivery after caesarean section. A further study failed to find a difference in head entrapment which also occurred at caesarean section (29). The trials in Grant's meta-analysis enrolled only 104 women. One of the Australian trials enrolled only two and both were randomised to the caesarean delivery group: difficulties in recruitment have also hampered the UK experience (30). Recruitment has failed because of the existence of pre-existing policies, many institutions choosing to deliver preterm breech babies by caesarean section.

Cord clamping

The time at which the umbilical cord is clamped is currently the subject of research investigation. One study has suggested that delayed cord clamping resulted in better short term outcomes (B) (31).

Place of delivery and transport

Every obstetric unit must have a clear protocol for the management of preterm labour.

Maternity units which are not staffed or equipped to provide neonatal intensive care should have specific guidelines for antenatal transfers of women with pregnancies at above average risk (B). Unexpected preterm delivery cannot be prevented and certain maternal conditions preclude in-utero transfer. Every maternity unit must have clearly established arrangements for the prompt, safe and effective resuscitation of such babies even if ongoing intensive care cannot be offered: see next section (C) (32).

Postnatal transfer of sick, preterm ventilated infants requires highly trained staff and specialised equipment. About 16 urgent transfers per 1,000 deliveries may be required, and the subject is currently under review at a national level (33).

Resuscitation

Inadequate resuscitation and poor early care makes RDS worse (B). Hypothermia reduces surfactant production and increases energy consumption, contributing to acidosis. Hypoxia and hypothermia interfere with the normal postnatal fall in pulmonary vascular resistance. Inadequate respiratory effort leads to a reduced functional residual capacity. Randomised controlled trials in this area are few and far between for obvious reasons. In one of the few studies which does exist, Drew showed better survival in preterm infants intubated from birth (34). This trial was not randomised. The working group considered that there was insufficient evidence to support routine intubation of *all* preterm infants (C). However, in the light of evidence in favour of prophylactic surfactant many local guidelines propose that all infants of less than 29 weeks gestation are intubated at birth and this is entirely reasonable good practice (C). Guidelines for neonatal resuscitation developed by the Royal College of Paediatrics and Child Health (RCPCH), and the RCOG have recently been published (35).

Personnel

All maternity units should have their own guidelines about who should be called to the delivery of preterm infants, and a training programme should be in place for these individuals (C). Those without training and expertise, who may be faced with an unexpected emergency, should have a clear action plan to use to call help (C).

Equipment

In order that resuscitation can take place quickly and effectively appropriate facilities and equipment must be available. A suitable list can be found in the publication “Resuscitation of babies at birth” published by the Royal College of Paediatrics and Child Health (BMJ Publications, 1997) which is endorsed by the BAPM (35).

Respiratory support during resuscitation

Babies with surfactant deficiency have particular difficulty in achieving adequate FRC and maintaining alveolar aeration. The ability to give sufficient inflation pressure and inflation time are thus especially important during resuscitation of preterm infants, and observation of chest movement remains the best guide to the correct inflation pressure (B). Physiological research has shown that inflation times of up to 5 seconds on the first breath may be required to achieve an adequate FRC (B) (36,37). Inflation pressures of 30-40 cm water may also be required on occasion (B)(38). Preterm infants who require anything other than minimal resuscitation should therefore be intubated to ensure full lung expansion and for the administration of prophylactic surfactant (C). The system employed to deliver air or oxygen via the endotracheal tube must be capable of delivering the pressure and inflation times required; if a self-inflating bag is used this means that the reservoir must have a capacity of at least 500 mls (B). Preterm infants who have required intubation should be transported to the neonatal unit with continued ventilatory support (C).

Choice of gas for resuscitation

Recent randomised controlled trials suggest that for infants of birthweight >999g air is equivalent to oxygen for resuscitation, with no more “resuscitation failures” (39). No studies limited to preterm infants have yet been done.

Use of drugs in resuscitation

Drugs are rarely needed in resuscitation and cannot substitute for effective ventilation, circulatory support and attention to temperature control. Drugs should never be given blindly into the umbilical cord.

Base

There is controversy about the need for bicarbonate or THAM to treat acidosis during resuscitation (40). The working group endorsed the RCPCH/RCOG guideline recommendation for treatment with sodium bicarbonate if the heart rate remains less than 60 beats per minute despite ventilation, chest compression and adrenaline (C). A cord or umbilical arterial pH can give a useful guide to the level of acidosis, allowing a calculation of the base deficit. A half correction for a base deficit of 20 mmol requires a dose of 4 mmol/kg

of bicarbonate (8.4% bicarbonate solution contains 1 mmol/ml). Both THAM and sodium bicarbonate can cause necrosis if they are allowed to extravasate into the tissues so a secure intravenous line is essential.

Glucose

Stressed preterm infants readily become hypoglycaemic and normoglycaemia should be maintained by careful monitoring, giving glucose as required. Boluses of glucose should be of 10%, 1 ml per kg is sufficient.

Adrenaline

There is little information about the role of adrenaline in the preterm neonate. In one study the use of adrenaline was associated with a poor outcome even if the infant survived the initial collapse (41). This is not an unexpected finding since a bradycardia refractory to straightforward resuscitation indicates a profound hypoxic insult has occurred. A dose of 10 micrograms/kg (0.1 mls/kg of 1:10,000 dilution) should be used if there is persisting bradycardia despite adequate ventilation and chest compression (C). In very preterm infants there may have been a prior decision, taken in conjunction with the baby's parents, not to offer more than basic resuscitation and this is appropriate in some cases (C). The first dose can be given via the trachea, but there is no certainty that this route is effective although adrenaline is absorbed this way (42)(B). At least one dose should be given intravenously if the baby remains bradycardic. A third larger dose of 100 micrograms/kg can be used in desperate circumstances.

Naloxone

Naloxone has no role in immediate care of the preterm infant except in the very unusual situation in which the mother has received opiate analgesia a few hours before delivery. In any case a preterm infant who is not breathing requires immediate respiratory support (C).

Albumin

Albumin has no place in the immediate care of the preterm infant. Unless there has been a significant fetomaternal hemorrhage the baby is not likely to be hypovolaemic, and in this situation blood is required. Albumin has recently been shown to be associated with an excess mortality when used in critically ill patients of all ages (43).

Early use of continuous positive airways pressure (CPAP) after resuscitation to ameliorate RDS severity

This subject remains controversial. Scandinavian groups and others have reported remarkable success with a combination of early CPAP, a "minitouch" technique and surfactant, avoiding artificial ventilation entirely (44) (45,46). The results were not replicated in the setting of a randomised controlled trial in term infants (47). A UK trial, co-ordinated from Manchester, is in progress.

Surfactant

In 1958, it was shown that babies who died from RDS had abnormal surfactant. Over the next decade there were a number of animal studies which showed that mature surfactant from animal lungs could be

concentrated and when placed in the lungs of immature animals improved their compliance, oxygenation, survival and reduced the lung damage when they were ventilated. During the 1980s and early 1990s there were many randomised controlled trials of surfactant therapy for the treatment of RDS, and there is now no doubt that this treatment is effective(48,49).

Intratracheal administration of surfactant to ventilated premature infants below about 30 weeks' gestation reduces the mortality and the incidence of air leaks by about 40%, and improves oxygenation and ventilation during the first 48-72 hours of life(48). There is little effect on the overall incidence of chronic lung disease, brain haemorrhages, patent ductus arteriosus or duration of ventilation. One meta-analysis suggested an increase in the incidence of pulmonary haemorrhage with synthetic surfactants although the overall incidence was low at 5% (50). These results were not confirmed in another meta-analysis (51).

Prophylactic versus rescue surfactant

Surfactant can be given immediately the baby is born "prophylactic treatment" or several hours later when the diagnosis of RDS has been established "rescue treatment".

There are seven randomised controlled trials that have compared prophylaxis with rescue treatment, and all used natural surfactant preparations(52). Treatment with surfactant at birth was more effective than when given a few hours later. The odds ratios (95% CI) in favour of prophylaxis were 0.59 (0.46 to 0.76) for neonatal mortality, 0.62 (0.42 to 0.89) for pneumothoraces and 0.54 (0.36 to 0.82) for pulmonary interstitial emphysema. The conclusion of the working party was that all babies born at less than 32 weeks' gestation should be given surfactant at birth if they need intubation because it saved about seven more lives for every 100 treated with rescue surfactant (B). Many neonatologists choose to intubate all infants less than 29 weeks gestation at birth in order to administer surfactant, and this is reasonable practice.

Surfactant preparations

Four surfactants are licensed in the UK for treating babies. They are animal derived surfactants and synthetic surfactants. The animal derived surfactants are Curosurf, which is an extract of pig lung mince and given in a volume of 1.25 to 2.5 ml/kg, and Survanta which is an extract of cow lung mince with three lipids added, given as a dose of 4 ml/kg. These surfactants contain apoproteins SP-B and SP-C that are thought to enhance their properties. Apoproteins SP-B and SP-C are present in different proportions from endogenous mature surfactant, and other apoproteins SP-A and SP-D are absent. The synthetic surfactants do not contain proteins. They are Exosurf which is a mixture of the key phospholipid DPPC, hexadecanol and tyloxapol given in a volume of 5 ml/kg, and ALEC which is a mixture of DPPC and phosphatidylglycerol given as a dose of 1.2ml regardless of size.

There have been fifteen studies comparing different surfactants, seven of which were of suitable quality for meta-analysis (53). Six of these trials compared Survanta and Exosurf, the other trial comparing Infasurf and Exosurf. The meta-analyses support a significant reduction in the risk of pneumothorax (0.69 CI 0.57 to 0.85), and showed a non-significant trend towards reduced mortality. Soll's conclusion was that, "on clinical grounds, natural surfactant extracts were the more desirable choice". The onset of action is more rapid with animal derived surfactants than artificial surfactants. This means that the babies treated with these surfactants need to be carefully monitored and their ventilator settings adjusted appropriately. Concern has been expressed because rapid effects lead to temporary changes in cerebral blood flow velocity and EEG recordings. There is currently no evidence to suggest that this more rapid onset of action has any deleterious effects. Administration of materials containing foreign animal proteins has also led to concerns of immunogenicity but as yet there is no evidence of a significant immunological disturbance. There is a theoretical risk of prion transmission although Survanta is prepared from New Zealand cattle, where BSE has not been identified; porcine products have not been associated with any transmitted prion disease. Short term changes in clinical state with deterioration in oxygenation, or extremely rapid improvement in overall condition following the administration of surfactant can occur. This appears to depend upon the type of surfactant and emphasises the need to gain local experience with the surfactants being used.

All the studies which have compared one dose with two or more have shown a better outcome with two doses (B). There is no evidence that four doses are better than two (54)(B). Surfactant treatment for babies as small as 500g has been little studied, but the benefits are considered to outweigh the risks (C). In larger babies, above 1250g, there is good evidence that surfactant treatment is effective for babies who develop RDS (55).

Ventilatory management

All infants at risk of RDS should be closely monitored for clinical and biochemical evidence of respiratory failure. Each unit that undertakes long term (≥ 24 hours) care of these infants should have at least one consultant paediatrician with an up to date knowledge of the principles of mechanical ventilation and who should be responsible for providing a clear respiratory management protocol for all the staff working on that unit. Particular attention must be paid to the provision of modern neonatal ventilators (see below) and efficient humidification systems.

Ventilation techniques

Continuous Positive Airway Pressure (CPAP)

CPAP improves oxygenation by increasing the functional residual capacity (FRC) through recruitment of collapsed alveoli. CPAP is indicated in babies with RDS who have a PaO_2 persistently below 7 kPa (50-60 mmHg) despite an increase in their inspired oxygen to 50% or above (C). Nasopharyngeal or endotracheal

CPAP alone is not generally suitable for small babies, who should be ventilated if they cannot maintain oxygenation. As discussed, although some units have success with the use of CPAP from very early in the course of the illness this is not a well evaluated therapy in the UK at present. However, in babies above 2 kg birthweight, or 32 weeks gestation, a period of nasopharyngeal CPAP can be tried as a response may avoid the need for ventilation. Close observation is essential and CPAP should only be continued if babies show adequate respiratory effort, and are maintaining satisfactory arterial blood gases.

Artificial ventilation

Indications for artificial ventilation in RDS include

- Deteriorating blood gases (see below)
- Cardiorespiratory collapse
- Persistent apnoeas and bradycardias

Institution of artificial ventilation should be considered if the PaO_2 is not maintained above 7 kPa in an inspired oxygen concentration of more than 50% (particularly in a baby below 32 weeks); and/or the PaCO_2 is rising to levels around 7 kPa particularly with a pH below 7.25 (C).

Choice of mechanical ventilator

Positive pressure ventilation in newborns is accomplished through either conventional ventilators or high frequency ventilators capable of cycling at rates above 150 per minute. Conventional ventilators are either “pressure” or “volume” type, and can be further classified on the basis of cycling mode – usually the way in which the inspiratory cycle is terminated. For example, in pressure limited time cycled ventilation mode, a peak inspiratory pressure is set and during inspiration gas is delivered to achieve the target pressure. After the target is reached the remainder of the gas volume is released into the atmosphere. As a result, the tidal volume delivery with each breath is variable despite recorded peak pressure being constant. In contrast, with volume limited modes, the pre-set volume is delivered with each breath regardless of the pressure that is needed. Some ventilators use gas flow as the basis of cycling mode in which inspiration ends when flow has reached a critical low or pre-set level (flow ventilators). There are now ventilators which provide the capability of using either volume or pressure controlled ventilation depending on the operator’s preference.

High frequency ventilation is usually delivered using high frequency oscillatory ventilators (HFOV). These are essentially airway vibrators (piston pump or vibrating diaphragm) that operate at frequencies at around 10 Hz (1 Hz = 1 cycle per second, 60 cycles per minute). During HFOV, inspiration and expiration are both active. A continuous flow of fresh gas (bias gas flow) rushes past the source that generates the oscillation and a controlled leak or low-pass filter allows gas to exit the system. Pressure oscillations within the airway produce a “tidal volume” of 2-3 ml around a constant mean airway pressure, which maintains lung volume in

a fashion equivalent to using very high levels of CPAP. The volume of gas moved in the “tidal volume” is determined by the amplitude of the airway pressure oscillation (ΔP).

Clinicians involved in the care of sick newborns must keep abreast of developments as it is likely that different types of ventilation (or respiratory) therapy will be shown to be more effective than others in specific clinical situations. Choosing an appropriate strategy will become more important than the type of ventilator used (v.i.).

Using conventional ventilation to treat RDS

Hypoxaemia in RDS is usually due to ventilation-perfusion (V/Q) mismatching or right to left shunting, although diffusion abnormalities and hypoventilation may also be additional factors. Oxygenation is directly related to FiO_2 and the mean airway pressure (MAP). MAP can be increased by changes in peak inspiratory pressure (PIP), positive end expiratory pressure (PEEP) or by changing the inspiratory-expiratory (I:E) ratio by prolonging the inspiratory time when the rate is kept constant. A very high MAP may cause over distension, and despite adequate oxygenation, oxygen transport may decrease due to reduced cardiac output. CO_2 elimination is directly proportional to minute ventilation, which is determined by the product of tidal volume (minus dead space ventilation) and breath rate. For the same minute ventilation, changes that alter tidal volume delivery usually are more effective in changing CO_2 elimination than those that alter breath rate because dead space ventilation remains constant.

Peak Inspiratory Pressure (PIP)

Changes in PIP affect oxygenation (by altering the MAP) and the $PaCO_2$ by effects on tidal volume and alveolar ventilation. An increase in PIP thus decreases $PaCO_2$ (\downarrow) and improves oxygenation ($\uparrow PaO_2$). PIP requirements should be determined by the compliance of the respiratory system and not by size or weight of the infant. The lowest PIP that adequately ventilates the patient as assessed by the clinical examination (chest movement and breath sounds) and blood gas analysis should be used. Inappropriately excessive PIP may cause lung overdistension and increase the risk of baro/volutrauma and hence air leak.

Positive End Expiratory Pressure (PEEP)

Adequate PEEP prevents alveolar collapse and by maintaining lung volume at end-expiration, improves V/Q matching. Increase in PEEP augments mean airway pressure and thus improve oxygenation. Nonetheless, use of a very elevated PEEP (more than 8 cm H_2O) does not benefit oxygenation and may induce hypercarbia by way of worsening the lung compliance and reducing tidal volume delivery because of overfilled alveoli ($\Delta P = PIP - PEEP$). High level of PEEP can also have adverse haemodynamic effect due to lung overdistension causing reduced venous return and hence cardiac output. Levels of 3 - 6 cm H_2O improve oxygenation in newborns with RDS without compromising lung mechanics, CO_2 elimination or haemodynamic stability (56).

Rate

Two basic methods exist which can be referred to as slow rate and fast rate. The slow rate method aims to start babies on the ventilator at rates of 30 - 40 breaths per minute (bpm). The fast rate method commences ventilation at about 60 bpm and the rate may be increased to 120 bpm if the baby is breathing at a faster rate

than the ventilator. The expiratory time should exceed the inspiratory time to prevent inadvertent alveolar overdistension, and inspiratory times should be limited to a maximum of 0.5 sec throughout the duration of mechanical ventilation except in unusual circumstances. Randomised controlled trials have shown a lower pneumothorax rate in infants ventilated at fast rates (57) (58), perhaps because at these rates artificial ventilation is more likely to synchronize with the infant's own respiratory effort (A). Inspiratory and expiratory times

These affect the gas exchange because of their relationship to the inspiratory and expiratory time constant of the lung. During the acute phase of RDS, the time constant is short and an inspiratory time between 0.3 - 0.5 seconds is adequate. Prolonging inspiratory time will increase the MAP and hence improve oxygenation and is an alternative as other manoeuvres such as increase in PIP. A prolonged inspiratory time will predispose to lung overdistension and air trapping as it is likely to reduce the expiratory time unless the rate is altered to account for the change.

Flow rate

Strictly speaking, a minimum flow of at least twice an infant's own minute ventilation (normal value 0.2 - 1 L/minute) should prove adequate, but in practise during mechanical ventilation, a flow between 4 - 10 L/minute is used. If higher respiratory rate or shorter inspiratory times are being used, flow rates at the upper end of the range may be needed to ensure delivery of intended tidal volume. A high flow rate produces a square waveform and improves oxygenation by its effect on MAP. The manufacturer's manual should be consulted to check the appropriate flow rate for the ventilator chosen; some types of valveless ventilators have a fixed flow rate of 5 l/min.

Surfactant failure

If the arterial oxygenation remains unacceptably low after two doses of surfactant then the infant has failed to respond to surfactant. Such infants are relatively rare and a cause should be sought. For example, the infant may have associated sepsis, pulmonary hypertension, a pneumothorax or pulmonary interstitial emphysema. Whilst considering alternative diagnoses, first increase the FiO₂ towards 90%, then increase the PIP and PEEP whilst continuing to observe chest movement. Obtain a chest X ray. Try to keep the inspiratory time at a level which achieves synchrony, but if the baby remains asynchronous in spite of sedation and analgesia paralysis should be considered. In paralysed infants the inspiratory time can be lengthened to 0.5 seconds or even longer provided the ventilator rate is reduced 30-60 breaths per minute. Once levels of PIP/PEEP of about 26/6 are reached further review of the baby's situation with an experienced neonatologist is vital. Some of these infants may respond to HFOV. Nitric oxide remains experimental in surfactant failure; one randomised controlled trial failed to show any effect in preterm infants with RDS (59). A multicentre study is in progress (INNOVO).

The infant's own respiratory activity

Breathing out of phase with the mechanical ventilator (sometimes called "fighting the ventilator") is agreed

to be a risk factor for a variety of complications such as ineffective gas exchange, air trapping, pneumothorax and intraventricular haemorrhage (B). There is no proven policy for the management of this problem, but the baby's need for ventilation should be reviewed. If continued mechanical ventilation is considered necessary, then sedation may reduce the babies respiratory activity or a non-depolarising muscle blocker should be used. Routine muscle relaxants for all ventilated babies are not advisable (B) (60). Alternatively the ventilator rate can be increased to 'capture' the respiratory rate of the baby or patient triggered ventilation (PTV) may be tried (61). There is no evidence to suggest that the use of ventilation rates above 150 bpm or oscillatory ventilation techniques are of benefit in this respect (C).

Patient-Triggered Ventilation (PTV)

One alternative with which to deal with the problem of asynchrony during IPPV is to use patient-triggered ventilation. In this mode of artificial ventilation the machine delivered breath is initiated in response to a signal derived from the patient's own inspiratory effort. Four signals have been utilised to provide PTV to the newborn; airway impedance, pressure and flow or measuring the infant's own activity via a Graesby capsule monitor attached to the upper abdomen. Each has inherent advantages and disadvantages (62). Patient-triggered ventilation is available in both pressure-limited and volume controlled modes. Despite earlier concern about the ability of smaller babies to trigger ventilation, the sophistication of the newer generation of ventilators allow the application of PTV to even the smallest babies. A recent large multicentre trial, enrolling almost 1000 babies, failed to show any advantage for PTV as the primary mode of ventilation in neonatal RDS. PTV was of no additional benefit using the ventilators employed in this study. Small randomised controlled trials have suggested that PTV is useful for weaning (B)(63), but the duration of ventilation in the large multicentre trial was the same for PTV or conventional ventilation. At the time of writing, therefore, PTV can only be recommended in infants with RDS who cannot achieve synchrony with fast rate conventional ventilation.

High frequency oscillation

Of the three oscillators available in the UK only the Sensormedics 3100/3100A has been used in randomised controlled trials. The other available oscillators are "add-on" modules for the Draeger and the SLE 2000 ventilator. Oscillators are powerful tools, and in "rescue" mode HFOV probably saves some infants with severe RDS who have failed to respond to conventional ventilation and surfactant (64). However, a systematic review concluded that the evidence was insufficient to prove that HFO was a better method of ventilation than conventional ventilation. HFOV was associated with fewer new air leaks but more intraventricular haemorrhages (65). Only one trial was included in this meta-analysis (66). HFOV is particularly effective in the management of hypercarbia.

What is even less certain than rescue treatment is the role of HFOV used as the primary mode of ventilation in RDS in very small babies who have received antenatal steroids and postnatal surfactant (67). The Provo trial (68) randomised 125 babies with RDS at less than 35 weeks gestation who had received surfactant.

Those who were ventilated with HFOV fared better than those ventilated conventionally in the short term, with more survivors without chronic lung disease at 30 days. Although there has been some concern about the high number of babies still ventilated at a month (half the HFOV group and all the conventionally ventilated group) the incidence of ultrasound abnormalities and retinopathy of prematurity was the same. Even this large study only enrolled 21 babies with a birthweight less than 1 kg. A meta-analysis of trials of high frequency ventilation revealed no difference in mortality or the incidence of chronic lung disease. The high incidence of IVH and PVL disappeared if the results of the large HiFi trial (which used a low volume strategy) were excluded, with a halving in the incidence of CLD (relative risk 0.43; 95% CI from 0.26 to 0.70) (69) (70). At the present time HFOV is reserved for rescue in most UK neonatal units (B), although a MRC sponsored trial of HFOV as the primary mode of ventilation in RDS has begun recruitment (the UK Oscillation Study UKOS). Contact UKOS@sghms.ac.uk.

Blood gas monitoring during RDS

There are two main reasons for monitoring blood gases. Firstly, as a guide to the appropriate level of ventilatory support and secondly, to minimise the risk of retinopathy of prematurity. Unfortunately, there is no agreement regarding “safe” arterial oxygen concentrations in this respect. It is therefore impossible to set absolute limits for blood gases. The frequent monitoring of blood gases is clearly essential during the acute stages of RDS to assess the need for or effect of respiratory support. This is most reliably achieved through umbilical artery catheterisation or by indwelling peripheral arterial cannulae. Monitoring of oxygen by arterial sampling from an indwelling arterial catheter is the 'gold standard' measurement and continuous monitoring by a catheter tip oxygen sensor is optimal. Non-invasive methods such as the use of transcutaneous oxygen and/or carbon dioxide tension monitors or pulse oximetry are useful trend detectors. These monitors should only be used in conjunction with blood sampling, balancing the known hazards associated with prolonged intravascular monitoring against the increased risks of ROP in very preterm babies subjected to high preductal arterial oxygen pressures in the first weeks of life. Pulse oximetry may be a useful guide to oxygenation during neonatal transport, but appropriate levels of arterial oxygen saturation (SaO₂) have not yet been agreed, and will vary according to the oximeter used. Acceptable levels for SaO₂ of 85-93 % have been proposed, but errors in the technique of measurement are potentially great and oximetry cannot be recommended as the only form of monitoring arterial oxygen levels in the early phases of RDS.

Hypocarbica is increasingly a problem in babies who have been treated with antenatal steroids, postnatal surfactant and ventilation from birth. Hypocarbica causes low cerebral blood flow, and a higher incidence of periventricular leukomalacia has been found in infants who had early hypocarbica (71). High frequency jet ventilation may be a particular culprit (72).

There is agreement on the following blood gas values (C):

pH: Avoid arterial pH levels of less than 7.25. Cellular metabolic function is likely to be compromised at levels below this.

PaO₂: The recommended range is 6 - 10 kPa. The lower acceptable limit of PaO₂ in an infant with RDS may be lower than this (around 5.6 kPa, 40 mmHg) provided oxygen delivery to the tissues is adequate as judged by haematocrit, peripheral perfusion, and base excess.

PaCO₂: More important than the PaCO₂ level is the pH and in general terms if this is maintained above 7.25 then the PaCO₂ is probably acceptable. Unless there is a specific reason for inducing hypocarbia the lower limit of PaCO₂ should be maintained above 5 kPa (37.5 mmHg).

General care during RDS

Prevention of infection

Differentiation of RDS from early onset septicaemia due to group B streptococcus is difficult, and the initial investigation of babies with RDS should include a blood culture. Many neonatologists commence antibiotic therapy whilst awaiting laboratory confirmation that infection was absent.

Fluid balance

RDS delays the onset of the normal postnatal diuresis and oedema often appears after 24-48 hours. Careful attention to fluid replacement therapy needs to be given to avoid fluid overload, which contributes to the complications of PDA and CLD.

Blood transfusion to replace blood loss

Preterm infants with RDS easily become anaemic from blood sampling, and replacement blood transfusion is often necessary for anaemia and/or hypotension. Replacement therapy should be considered when the PCV is less than 35-40%.

Intensive care monitoring

Successful treatment of RDS requires careful monitoring and attention to the details of intensive care support which preterm babies require. This includes frequent monitoring not only of blood gas concentrations but also of electrolyte levels and blood glucose. Monitoring of heart rate, respiration, temperature and blood pressure are the minimum requirements for a ventilated baby with RDS. Continuous monitoring of oxygen levels using transcutaneous monitors or an indwelling oxygen electrode has already been discussed.

Endotracheal suction

Endotracheal suction to maintain airway patency is a necessary component of care for the intubated neonate and is frequently carried out as a routine nursing practice. The primary purpose of endotracheal suction is to

remove airway secretions, thereby preventing obstruction, atelectasis and decreased lung compliance, whilst optimising oxygenation and ventilation. Many deleterious physiological consequences are known to be associated with endotracheal suction. Researchers have documented bacteraemia, hypoxaemia, tachycardia and bradycardia, atelectasis, systemic hypertension and raised intracranial pressure. A randomised controlled trial has shown that routine suctioning had no advantages (73). Suctioning the endotracheal tube in babies with RDS should be instituted only when secretions begin, usually after 48 hours of age, and should be kept to a minimum (B).

Warming and humidifying inspired gases can help to reduce the problem of tube blockage. This can be achieved by setting the delivered gas temperature to 37 degrees C, whereby a minimum of 38 mg/l of water (equivalent to 100% Relative Humidity) results.

Closed systems of suction introduced in the 1970's permit suctioning to take place without the need for disconnection from the ventilator. These are now widely available for use with adults, but research and application to neonatal use has been very limited.

The potential benefits would appear to be maintenance of positive pressure ventilation, the stability of PEEP, and the continuation of oxygen supply. The system has not been widely adopted, probably due to concern about infection, the extra workload of pre-determining the length of suction catheter to pass and the duration of suction time.

Physiotherapy

Chest physiotherapy As with endotracheal suction, debate exists as to the timing, frequency and duration of chest physiotherapy. Indeed, examination of the available literature reveals very few studies of physiotherapy for the preterm infant to support clinical practice (74). Physiotherapy contravenes the minimal handling concept. Routine chest physiotherapy is not recommended in neonatal RDS (C). Postural physiotherapy once handling tolerated prevents contractures especially for infants who are paralysed.

Nursing Position for ventilated infants with RDS

The supine position allows unrestricted access to the baby for intubation, cannulation and other procedures. The supine position also affords the opportunity for clear visual assessment of chest wall movement and symmetry, and the site of the umbilical arterial catheter. Keeping the head in constant slight extension stabilises endotracheal tube position, which reduces the risk of laryngeal trauma. Supine positioning is not optimal in terms of oxygenation and energy expenditure, for which the prone position is better. Some workers report an increased neck hyperextension and shoulder elevation in infants who had been supine for a prolonged period (75). Head flattening and excessive hip flexion are also a problem. For infants who require prolonged ventilation, there is evidence to suggest benefit from the supported position (76). The aim of this form of nursing care is to encourage a balance between flexion and extension in a variety of positions both prone, supine and lateral.

Complications of RDS and their prevention

Cardiovascular system

Blood pressure

Intravascular blood pressure monitoring is the ideal, but non-invasive blood pressure measurement using the Doppler technique can give a reliable estimate of systolic pressure in relatively well babies. The most commonly used 'normal range' for babies weighing less than 1000g is derived from a study of only 16 relatively stable babies (77). The average mean blood pressure (MBP) in the first 12 hours of life was 33 - 34 mmHg, with a linear relationship between blood pressure and birth weight. The lower limit of normal was 24mmHg at 750g, and 25 mmHg at 1000g. This lower limit of normal corresponds to the 10th percentile in a study of 131 very low birth weight (VLBW) infants with RDS, in which birth weight specific regressions for MBP on postnatal age were computed (78). Hypotension has been associated with an increased incidence of cerebral haemorrhage and mortality in babies with RDS. The Working Group suggests that good clinical practice includes measurement of the blood pressure in neonates with RDS, with prompt treatment of hypotension when it is accompanied by evidence of poor tissue perfusion (C).

The first line of treatment should be with volume expansion, although it is important to remember that there is a poor relationship between blood pressure and blood volume in the newborn (79,80). Saline is as effective as plasma in increasing the circulating volume (B), and avoids any concern about adverse effects of albumin (81). Routinely administered volume expansion was not effective in reducing the incidence of intracranial haemorrhage (82). 10-20 mls per kg of saline or colloid leads to a small but significant increase in blood pressure which may not be sustained, and about 60% of babies given volume expansion will subsequently require inotropic support. Unless there is clear evidence of hypovolaemia, massive capillary leak or blood loss repeated volume expansion is likely to be counter-productive, especially if the cause of the hypotension is myocardial dysfunction or PDA. Early use of dopamine was more successful in increasing the blood pressure than colloid in one RCT (83). Myocardial dysfunction is present in many hypotensive infants with RDS and can be demonstrated with echocardiography (84). In addition, a large PDA is related to a lower mean blood pressure (85).

Second line treatment involves inotropic support. Dopamine was more effective than dobutamine at increasing the mean blood pressure in three randomised controlled trials enrolling 123 preterm infants (B) (86,87) (88). Dopamine works by increasing the systemic vascular resistance, whereas dobutamine increases the left ventricular output. Most infants respond to dopamine in a dose of 10 micrograms per kg per minute; doses above 15 micrograms per kg per minute increase pulmonary vascular resistance thus exacerbating pulmonary hypertension and are not recommended.

Third line treatment is reserved for resistant cases. The effect of adding dobutamine (in a dose of 10-20 micrograms per kg per minute) to dopamine should be tried first. After this treatment is experimental. Hydrocortisone was effective when compared to dopamine in one randomised controlled trial (89). Adrenaline and isoprenaline can be tried.

Management of delayed closure of the ductus arteriosus

Constriction and closure of the ductus is normally complete within the first 48 hours in term infants and in preterm infants without respiratory distress. A haemodynamically significant PDA developed in 36% of ventilated preterm infants in one study (90). The duct is usually clinically silent in the early neonatal period, but echocardiography on the first day has shown that in infants where the PDA subsequently becomes symptomatic the diameter is greater than 1.5 mm (91). Antenatal steroids protect against symptomatic PDA. Prophylactic indomethacin has been shown to protect against GMH-IVH, an effect which may be mediated by early ductal closure (92). Unfortunately this benefit did not translate into improved neurodevelopmental outcome at 3 years (93). Prophylactic indomethacin has not been widely adopted in the UK in spite of meta-analyses confirming benefit against GMH-IVH and symptomatic PDA (94). Targetted therapy, restricting very early indomethacin to the group of babies with a PDA of diameter more than 1.5 mm on the first day, is an attractive option but has yet to be tested.

Symptomatic PDA should be treated with indomethacin unless there are contraindications (renal failure, thrombocytopenia, necrotising enterocolitis). There are several alternative dosage schedules including 0.1 mg/kg daily for 6 days or 0.2 mg/kg 12 hourly for three doses. The renal effects of indomethacin must be anticipated.

Growth failure

Adequate nutrition is an important part of the management of RDS (C). Facilities for total parenteral nutrition must be available, but minimal enteral feeding should be considered in infants with stable or improving RDS (C). Raw maternal breast milk protects against necrotising enterocolitis and is the best choice for minimal enteral feeding (B) (95). There is no evidence that uncomplicated umbilical arterial catheterisation increases the risk of necrotising enterocolitis.

Chronic lung disease

This has been defined as the requirement of supplementary oxygen after 28 days from birth, or an additional oxygen requirement in a prematurely born infant after 36 weeks postmenstrual age. Management options include:

Steroids

Exogenously administered steroid (usually dexamethasone) has been shown to reduce the duration of mechanical ventilation in preterm infants and should be considered in babies with persisting lung disease at two weeks of age. At least five randomised trials confirm the efficacy of steroids used in this way, although the conclusion of a meta-analysis was that the benefits of steroid therapy between 7 and 14 days may not outweigh the side effects (96). Halliday also reviewed very early (<96 hours) and late (>3 weeks) treatment for the Cochrane collaboration, reaching the same conclusions. Concern has been raised about the long term effects of very early treatment, with one study showing that dexamethasone treated boys were shorter and

lighter at 2 years, with more neurologic deficit in the treated infants (97). “Pulse” or inhaled steroid therapies are not yet fully evaluated either. Treatment at four weeks of age may be equally effective as that at two weeks, and less hazardous (98), (99).(43,100,101)

Steroid treatment is usually given initially be given as a short course, beginning with 500 micrograms per kg per day. The duration of treatment in the trials included in the meta-analysis of Halliday varied from two to 42 days. There is some evidence to support continuing treatment , with a tapering regimen in babies who respond (B). Response is usually evident within 48 hours of starting treatment. Whilst the rapid improvement in pulmonary compliance which is observed after steroid therapy usually allows a reduction in ventilator settings and facilitates weaning from artificial ventilation, the use of steroids does not alter mortality or long-term outcome (102). Steroids are associated with many acute side-effects including hypertension, hyperglycaemia, diminished weight gain and head growth.

Diuretics

There is no evidence of benefit from long-term diuretic treatment, although episodes of cardiac failure associated with CLD should be treated with diuretics. Loss of calcium and salt are important side-effects of long-term diuretic use and regimens should be tailored to minimise and monitor this. Not frusemide.

Methylxanthines

There is no evidence to suggest that long-term methylxanthine treatment improves outcome, although these drugs are valuable as an adjunct to assist weaning from ventilation and in prophylaxis against apnoea.

Oxygen

Oxygen is essential in the management of CLD. Inadequate oxygen therapy is associated with the development of pulmonary hypertension which can cause left and right heart failure. Oxygen therapy reduces apnoea and bronchospasm. Once the infant has reached 36 weeks postconceptional age the risk of ROP has abated and oxygen tensions should be maintained at the higher end of the normal range. Saturation monitoring is useful at this stage, and levels of 92-96% are probably optimal, although the results of a current Australian prospective RCT comparing the outcome in CLD for two groups of infants, maintained at 95-97% or 91-93% will assist this debate. Regular monitoring during all aspects of activity is important.

Follow up

Hospital outcome for babies with RDS should be monitored as part of routine data collection. The BAPM dataset is recommended as the minimum information to collect about all babies who require admission to a neonatal unit. Most children with RDS will have no long term sequelae from their neonatal respiratory illness. However, RDS in very preterm babies is associated with an increased frequency of neurological sequelae. Children with CLD are at particular risk of continuing respiratory morbidity with persisting symptoms of cough and wheeze (103). They have a high chance of readmission and a need for further mechanical ventilation after discharge home. Respiratory syncytial virus is a particular risk, and

consideration should be given to prophylaxis against epidemics. Good practice is to follow up very preterm children for at least two years, in order to monitor respiratory symptoms and to screen for neurodevelopmental problems. Each unit should have a defined protocol for follow up and close liason with child development teams in the locality, and in addition should ascertain the later health status of such survivors on a local and geographical basis. Standard definitions of severe disability are available for two year old children, including measures of respiratory disability, which should be monitored and reported in annual reports.

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