Introduction:

The European Consensus Guideline on the Management of Neonatal Respiratory Distress Syndrome (RDS) in Preterm Infants – 2013 Update¹ is summarised below for the Wales Neonatal Network. For the purpose of this guideline, preterm infants are defined as those born at <34 weeks’ completed gestation. References to other relevant publications/guidelines or pre-existing Wales Neonatal Network Guidelines are made through the text where appropriate, and should be referred to for further advice.

This guideline is split into two sections according to the strength of evidence supporting them. The first section covers recommendations supported by high quality evidence (Grade A evidence). It is suggested that these recommendations should be carried out for all preterm infants with RDS. The second section covers recommendations from Grade B-D evidence. While a wide range of clinical situations are covered in this guideline, we advise seeking senior help if in doubt. These guidelines can be modified for use in local units.

High Quality Evidence (Grade A Recommendations):

Prenatal Care:
- Clinicians should offer a single course of prenatal corticosteroids to all women at risk of preterm delivery from about 23 weeks up to 34 completed weeks gestation.
- A second course of antenatal steroids may be appropriate if the first course was administered more than 2 – 3 weeks earlier and the infant is still <33 weeks’ gestation when an obstetric situation arises.
- Antibiotics should be given to mothers with preterm pre-labour rupture of membranes as this reduces the risk of preterm delivery.
- Maternal magnesium sulphate infusion for neuroprotection of the foetus should be considered for all pregnant women who are in established preterm labour or having a planned preterm birth within 24 hours, between 24-30 weeks’ gestation, and possibly up to 34 weeks’ gestation.
- Clinicians caring for the mother should follow NICE guidelines on management of preterm labour and birth (NG25²).

Delivery Room Stabilisation:
- If possible delay clamping of the umbilical cord for at least 60 seconds with the infant held below the mother to promote placental-to-foetal transfusion. Please also refer to NICE Guideline NG25².
- In spontaneously breathing infants stabilise with CPAP of at least 5-6 cmH₂O via facemask or nasal prongs⁶.
- Intubation should be reserved for infants who have not responded (bradycardia, poor respiratory effort, apnoea etc.) to positive pressure ventilation via a facemask. Infants who require intubation for stabilisation should be given surfactant.
- Plastic bags or occlusive wrapping under radiant warmers should be used during stabilisation in the delivery suite for infants <28 weeks’ gestation to reduce the risk of hypothermia.

Surfactant Therapy:
- Infants with RDS should be given a natural surfactant preparation.
- A policy of early rescue surfactant should be standard but there are occasions when surfactant should be administered in the delivery suite, such as extremely preterm infants in whom the mother has not had antenatal steroids or those who require intubation for stabilisation.
- Porflectant alfa (Curosurf®) in an initial dose of 200mg/kg is better than 100mg/kg of porflectant alfa or beractant for treatment of RDS.
- A second, and sometimes a third, dose of surfactant should be administered if there is evidence of ongoing RDS such as a persistent oxygen requirement and need for MV. Please liaise with senior colleagues for advice on timing of repeat surfactant doses.

Non-Invasive Respiratory Support:
- CPAP should be started from birth in all infants at risk of RDS, such as those <30 weeks’ gestation who do not need MV, until their clinical status can be assessed.
- The system delivering CPAP is of little importance; however, the interface should be short bi-nasal prongs or mask and a starting pressure of at least 6cmH₂O should be applied.
- CPAP with early rescue surfactant should be considered the optimal management for infants with RDS.
- A trial of NIPPV can be considered to reduce the risk of extubation failure in infants failing on CPAP; however, this may not offer any significant long-term advantages.
**Mechanical Ventilation Strategies:**
- Targeted tidal volume ventilation should be employed as this shortens duration of ventilation and reduces BPD. Please refer to Wales Neonatal Network Ventilation Guideline.
- Caffeine should be used in all infants with apnoea and to facilitate weaning from MV.
- A short tapering course of low- or very low-dose dexamethasone should be considered to facilitate extubation in infants who remain on MV after 1-2 weeks.

**Prophylactic Treatment of Sepsis:**
- In units with a high rate of invasive fungal infection, prophylaxis with fluconazole is recommended in infants <1000g birth weight or ≤27 weeks’ gestation, starting on day 1 of life with 3mg/kg twice weekly for 6 weeks. Please follow your local unit policy on fungal prophylaxis.

**Supportive Care:**
- If a decision is made to attempt therapeutic closure of the PDA then indomethacin or ibuprofen have been shown to be equally efficacious, although there is less of transient renal failure or NEC with ibuprofen.

**Miscellaneous Considerations:**
- Inhaled nitric oxide is not beneficial in the management of preterm infants with RDS.

**Grade B-D Recommendations:**

**Prenatal Care:**
- Women at high risk of very preterm birth should be transferred to perinatal centres with experience of management of RDS (C).
- Antenatal steroids should also be considered for women undergoing an elective caesarean section prior to labour up to 39 weeks’ gestation (B).
- Clinicians should consider short-term use of tocolytic drugs to allow completion of a course of prenatal corticosteroids and/or in-utero transfer to a perinatal centre (B).
- Clinicians caring for the mother should follow NICE guidelines on management of preterm labour and birth (NG25).

**Delivery Room Stabilisation:**
- Oxygen for resuscitation should be controlled using a blender. A concentration of 21-30% oxygen is appropriate to start stabilisation and adjustment up or down should be guided by applying pulse oximetry to the right wrist from birth to give information on the heart rate and saturations (B).
- Infants stabilised under a radiant warmer should be in a servo-controlled thermal environment (e.g. transport incubator) within 10 minutes to avoid overheating (B).

**Surfactant Therapy:**
- Infants with RDS should be given rescue surfactant early in the course of the disease. A suggested threshold would be to treat infants <26 weeks’ gestation when FiO₂ requirements >0.30 and infants >26 weeks when FiO₂ requirements >0.40 (B).
- Consider the InSurE technique. More mature infants can often be extubated to CPAP or NIPPV immediately following surfactant, and a clinical judgment needs to be made as to whether an individual infant will tolerate this (B).

**Oxygen Supplementation beyond Stabilisation:**
- In preterm infants receiving oxygen, the saturation target should be between 91 and 95% (B). Saturation monitor alarm limits should be set to a low of 90% and a high of 96%.
- After giving surfactant a hyperoxic peak should be avoided by rapid reduction in FiO₂ (C).
- Fluctuations in SaO₂ should be avoided in the postnatal period (C).

**Non-Invasive Respiratory Support:**
- After CPAP 6cmH₂O has been started, CPAP level can then be individualised depending on clinical condition, oxygenation and perfusion (D).

**Mechanical Ventilation Strategies:**
- MV should be used to support infants when other methods of respiratory support have failed (B). Duration of MV should be minimised to reduce its injurious effects on the lung (B).
- HFOV may be useful as a rescue therapy (B).
- When weaning from MV it is reasonable to tolerate a moderate degree of hypercarbia, provided the pH remains above 7.22 (B).
Avoid hypocarbia as this is associated with increased risk of BPD and periventricular leukomalacia (B).

Caffeine should also be considered for infants at high risk of needing MV, such as those <1250g birth weight who are managing on non-invasive respiratory support (B).

Please also refer to Wales Neonatal Network Ventilation Guideline.

**Prophylactic Treatment for Sepsis:**

- Antibiotics are often started in infants with RDS until sepsis has been ruled out, but policies should be in place to narrow the spectrum and minimise unnecessary exposure. A common regime includes penicillin or ampicillin in combination with an aminoglycoside (D). Antibiotics should be stopped as soon as possible once sepsis has been excluded (C). Please also refer to NICE Guideline CG149 Neonatal Infection: Antibiotics for Prevention and Treatment.

**Supportive Care:**

- Body temperature should be maintained at 36.5-37.5°C at all times (C).
- Most infants should be started on IV fluids of 70-80ml/kg/day while being kept in a humidified incubator, although some very immature infants may need more (D).
- Fluids must be tailored individually according to the serum sodium levels and weight loss (D).
- 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).
- Parenteral nutrition should be started on day 1 to avoid growth restriction and quickly increased to 3.5g/kg/day of protein and 3.0g/kg/day of lipids as tolerated (C).
- Minimal enteral feeding should also be started from the first day (B). Please also refer to Wales Neonatal Network Enteral Feeding Guideline for Preterm Infants.
- Treatment of arterial hypotension is recommended when it is confirmed by evidence of poor tissue perfusion (C). If hypotension is suspected, please seek senior support to advise on further management.
- Haemoglobin concentration should be maintained within normal limits (D). Please follow your local guidelines on management of anaemia.

**Miscellaneous Considerations:**

- Elective caesarean section in low-risk pregnancies should not be performed before 39 weeks’ gestation (B).
- Surfactant therapy can be used to improve oxygenation following pulmonary haemorrhage but there may be no long term benefits (C).
- Surfactant replacement for evolving BPD leads only to short-term benefits and cannot be recommended (C).

The existing Wales Neonatal Network Guideline: PrimeTime; Resuscitation and early care of extremely premature infants <28 weeks gestation, also considers many of the issues discussed above.

**NICE NG25 Guideline:**

Additionally, NICE have published guidelines on the management of preterm labour and birth in November 2015, which makes the following recommendations relevant to this RDS guideline.

- Offer women with preterm prelabour rupture of membranes (PPROM) oral erythromycin 250 mg 4 times a day for a maximum of 10 days or until the woman is in established labour (whichever is sooner).
- Use of tocolysis in preterm labour:
  - Consider nifedipine for tocolysis for women between 24+0 and 25+6 weeks of pregnancy who have intact membranes and are in suspected preterm labour.
  - Offer nifedipine for tocolysis to women between 26+0 and 33+6 weeks of pregnancy who have intact membranes and are in suspected or diagnosed preterm labour.
- Antenatal corticosteroids:
  - Consider maternal corticosteroids for women between 24+0 and 25+6 weeks of pregnancy who are in suspected or established preterm labour, are having a planned preterm birth or have PPROM.
  - Offer maternal corticosteroids to women between 26+0 and 33+6 weeks of pregnancy who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have PPROM.
  - Consider maternal corticosteroids for women between 34+0 and 35+6 weeks of pregnancy who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have PPROM.
  - Do not routinely offer repeat courses of maternal corticosteroids, but take into account:
    - The interval since the end of last course
    - Gestational age
    - The likelihood of birth within 48 hours.
• Intravenous Magnesium Sulphate:
  o Offer intravenous magnesium sulfate for neuroprotection of the infant to women between 24+0 and 29+6 weeks of pregnancy who are in established preterm labour or having a planned preterm birth within 24 hours.
  o Consider intravenous magnesium sulfate for neuroprotection of the infant for women between 30+0 and 33+6 weeks of pregnancy who are in established preterm labour or having a planned preterm birth within 24 hours.

• Timing of cord clamping:
  o If a preterm infant needs to be moved away from the mother for resuscitation, or there is significant maternal bleeding, consider milking the cord and clamp the cord as soon as possible.
  o Wait at least 30 seconds, but no longer than 3 minutes, before clamping the cord of preterm infants if the mother and infant are stable.
  o Position the infant at or below the level of the placenta before clamping the cord.

Glossary of Terms in Guideline:
‘Respiratory Distress Syndrome (RDS)’: A condition of pulmonary insufficiency that in its natural course commences at or shortly after birth and increases in severity over the first two days of life. Clinically, RDS presents with early respiratory distress comprising cyanosis, grunting, retractions and tachypnoea. Respiratory failure may develop, indicated by blood gas analysis, and the diagnosis can be confirmed on chest X-ray with a classical ‘ground glass’ appearance and air bronchograms. RDS is due to a deficiency of alveolar surfactant and immaturity of the lungs, and it is mainly, but not exclusively, a disease of preterm infants.
‘Early rescue surfactant’: Used in infants who have not been prophylactically intubated and given surfactant at birth, but who are initially stabilised on CPAP, develop signs of worsening RDS, and are subsequently given surfactant via an endotracheal tube.
‘InSurE’: Technique for the delivery of early rescue surfactant. The infant is intubated with an endotracheal tube and surfactant is administered. Following surfactant administration, the infant is stabilised and then extubated after a variable, but short, period of time, and continues on non-invasive respiratory support.
‘BPD’: Bronchopulmonary dysplasia. A histological consequence of respiratory distress syndrome, mechanical ventilation and long-term oxygen use. Also called chronic lung disease (CLD)
‘NEC’: Necrotising Enterocolitis.
‘MV’: Mechanical ventilation.
‘HFOV’: High frequency oscillatory ventilation.
‘NIPPV’: Nasal Intermittent Positive Pressure Ventilation.
‘CPAP’: Continuous Positive Airways Pressure.
‘SaO\textsubscript{2}’: Percentage oxygen saturation.
‘NICE’: National Institute for Health and Care Excellence.

Summary of Grades of Evidence:

<table>
<thead>
<tr>
<th>GRADE</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>At least one meta-analysis, systematic review or high-quality RCT with low risk-of-bias, directly applicable to the target population.</td>
</tr>
<tr>
<td>B</td>
<td>A body of evidence including systematic reviews of case-control or cohort studies, high-quality case-control or cohort studies with very low risk of confounding bias, directly applicable to the target population and demonstrating consistency of results.</td>
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<tr>
<td>C</td>
<td>A body of evidence including high-quality case-control or cohort studies with low risk of confounding bias, directly applicable to the target population and demonstrating consistency of results.</td>
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<tr>
<td>D</td>
<td>Non-analytic studies e.g. case reports or case series, or expert opinion.</td>
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References:

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