

European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update.

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provided that proper credit is given to the author and the original publisher. Respiratory distress
syndrome (RDS) care pathways evolve slowly as new evidence emerges. We report the sixth
version of "European Guidelines for the Management of RDS" by a panel of experienced European
neonatologists and an expert perinatal obstetrician based on available literature up to end of 2022.
Optimising outcome for babies with RDS includes prediction of risk of preterm delivery, appropriate
maternal transfer to a perinatal centre, and appropriate and timely use of antenatal steroids.
Evidence-based lung-protective management includes initiation of non-invasive respiratory support

from birth, judicious use of oxygen, early surfactant administration, caffeine therapy, and avoidance of intubation and mechanical ventilation where possible. Methods of ongoing non-invasive respiratory support have been further refined and may help reduce chronic lung disease. As technology for delivering mechanical ventilation improves, the risk of causing lung injury should decrease, although minimising time spent on mechanical ventilation by targeted use of postnatal corticosteroids remains essential. The general care of infants with RDS is also reviewed, including emphasis on appropriate cardiovascular support and judicious use of antibiotics as being important determinants of best outcome. We would like to dedicate this guideline to the memory of Professor Henry Halliday who died on November 12^[,] 2022. These updated guidelines contain evidence from recent Cochrane reviews and medical literature since 2019. Strength of evidence supporting recommendations has been evaluated using the GRADE system. There are changes to some of the previous recommendations as well as some changes to the strength of evidence supporting recommendations that have not changed. This guideline has been endorsed by the European Society for Paediatric Research (ESPR) and the Union of European Neonatal and Perinatal Societies (UENPS).

pmc-status-qastatus 0 pmc-status-live yes pmc-status-embargo no pmc-status-released yes pmc-prop-open-access yes pmc-prop-olp no pmc-prop-manuscript no pmc-prop-legally-suppressed no pmc-prop-has-pdf no pmc-prop-has-supplement no pmc-prop-pdf-only no pmc-prop-suppress-copyright no pmc-prop-is-real-version no pmc-prop-is-scanned-article no pmc-prop-preprint no pmc-prop-in-epmc yes pmc-license-ref CC BY Introduction Survival of preterm infants continues to improve, with those at 22–23 weeks of gestation now having reasonable chances of making it home to their families [1]. There is a growing trend towards offering initial life support to infants born at lower perceived levels of viability, which in some countries is now defined as low as 22 weeks of gestation [2]. However, we caution that recommendations given in these guidelines are based on evidence from studies, which almost without exception, have been generated in times where the resuscitation of the most preterm infants was not often attempted, and until very recently, infants of the lowest gestations were not included in clinical trials. We therefore recommend caution when applying current recommendations to the most preterm infants with respiratory distress syndrome (RDS). Until more evidence is available, these guidelines apply mainly to management of RDS in infants with gestational ages of greater than 24 weeks. Managing RDS remains a key component of neonatal intensive care. European data from 2014 to 2016 show that around 50% of all babies born between 22 +0 and 32 +6 weeks receive surfactant; therefore, relevant skills for surfactant administration and mechanical ventilation (MV) remain important [3].

RDS is caused by pulmonary immaturity and surfactant deficiency, resulting in respiratory insufficiency from soon after birth. There is now less emphasis on radiographic diagnosis and grading of RDS, such as “ground glass with air bronchograms.” Definitions based on blood gas analyses are also redundant, as management has moved towards an approach of pre-emptive treatment with surfactant based on clinical assessment of work of breathing and inspired oxygen requirement to avoid worsening RDS. The aim of modern RDS management is to maximise survival while minimising complications such as air leaks and BPD. Many strategies for prevention and treatment of RDS and providing early respiratory support have been tested in clinical trials and are summarised in updated systematic reviews, all of which inform these guidelines. This current version updates previous versions [4 , 5 , 6 , 7 , 8] after critical examination of the most recent evidence available to end of 2022. We have again used a format of summarising management strategies followed by evidence-based recommendations according to the GRADE system to reflect the authors' judgement of the evidence supporting each of the statements (Table 1). [9]. Summary of recommendations is shown in Table 2 .

Lack of antenatal care increases risk of death or severe morbidity [10]. General measures to reduce preterm birth include prevention of teenage pregnancies, adequate pregnancy spacing, prevention of unnecessary caesarean sections, early screening for preeclampsia and treatment with low-dose aspirin in women at risk, and single embryo transfer when in vitro fertilisation is used [11].

In asymptomatic pregnant women at risk of spontaneous preterm birth, due either to previous preterm birth or where a shortened cervix has been identified, use of progesterone is associated with a reduced rate of preterm birth and lower perinatal mortality [12]. This holds for singleton pregnancies only, as there are insufficient data on twins. Results for neonatal outcomes, including risk of RDS, were favourable but less certain [13]. Large trials have questioned the efficacy of progesterone in the absence of a short cervix, and there is very little evidence of benefit beyond the neonatal period. Routine cervical length measurements are advised in populations at risk of preterm birth and those with an overall low risk and/or very low incidence of short cervix, provided there is adequate quality assurance in measuring cervical length [12]. Cervical cerclage may also reduce preterm birth in high-risk singleton pregnancies [14]. The challenge is to identify high-risk pregnancies early and aim for effective prevention of preterm birth. The same holds for omega-3 fatty acid supplementation, which may also reduce preterm delivery [15] but most likely only in populations with poor nutrition.

Interventions to improve outcomes and prevent RDS begin before birth. There is often warning of impending preterm delivery and a need to consider interventions to prolong gestation or reduce risk of adverse outcomes by “preparing” the foetus. Cervical length measurement, possibly in combination with a biomarker [16], may determine which women are at risk of delivery within 7 days, perhaps allowing more judicious use of antenatal treatments. Preterm fetuses with expected delivery before 30 weeks of gestation should, where possible, be transported in utero to tertiary centres where appropriate skills are available; best outcomes are achieved for babies born in centres with a high throughput of VLBW babies [17]. In prenatal pre-labour rupture of membranes, antibiotics can delay preterm delivery and reduce neonatal morbidity, although co-amoxiclav should be avoided because of its association with increased risk of necrotising enterocolitis (NEC) [18]. Magnesium sulphate, given to women with imminent preterm delivery before 32 weeks, reduces incidence of cerebral palsy at 2 years by about 30%, although longer term benefits are unclear [19]. A reduction in cerebral palsy may be obtained if magnesium sulphate is given as close to 4 hours before delivery, so advanced dilatation is not a contraindication to treatment [19]. Overdosing must be avoided given maternal side effects such as vasodilatation and neuromuscular blockage. Tocolytic drugs can be used in the short term to delay birth, allow safe transfer to a perinatal centre, and allow prenatal corticosteroids time to take effect, although tocolytics have no direct beneficial effect on the foetus [20]. There is little evidence that delivering preterm infants by CS rather than allowing vaginal delivery improves outcome.

A single course of prenatal corticosteroids given to mothers with anticipated preterm delivery before 34 weeks of gestation improves survival; reduces RDS, NEC, and IVH; and is not associated with any significant maternal or short-term foetal adverse effects [21]. These favourable results were shown in the 1970s but also in clinical trials performed after 1990, indicating that even with modern neonatal care, prenatal steroids are beneficial. Prenatal corticosteroid therapy is recommended in all pregnancies with threatened preterm birth before 34 weeks of gestation where active care of the newborn is anticipated. Although there are limited RCT data in babies <25 weeks of gestation, observational studies suggest that antenatal corticosteroids, together with other active management practices, reduce mortality even down to 22 weeks [22], and current guidelines have incorporated these data in their recommendations [23]. In pregnancies between 34 and 37 weeks of gestation, prenatal steroids will also reduce risk of short-term respiratory morbidity, but not mortality, and there is increased risk of neonatal hypoglycaemia [24]; benefits reduce with increasing gestation, whereas the incidence of hypoglycaemia increases [25]. In women in spontaneous preterm labour after 34 weeks, steroid treatment is controversial and not advisable [26], as exposure is associated with a significantly higher risk of adverse neurocognitive and psychological outcomes [27]. Optimal treatment to delivery interval is more than 24 hours and less than 7 days. Beyond 7–14 days, benefits are diminished. In a cohort study, the beneficial effect of the first dose of antenatal steroids on very preterm infants starts within a day, so advanced dilatation is not a contraindication [28]. There is still debate about whether steroids should be repeated 1 or 2 weeks after the first course for women with threatened preterm labour. A repeat course reduces the risk of needing respiratory support but does not affect mortality or other serious

health outcomes and reduces birth weight and head circumference [29]. The WHO recommends that a single repeat course of steroids be considered if preterm birth does not occur within 7 days after the initial course and there is a high risk of preterm birth in the next 7 days. None of the clinical trials showed any improved outcomes when the repeat course had been given after 32 weeks; a single repeat course should therefore be restricted to gestational age <32 weeks [30]. Most studies showing benefit include mixed populations of singleton and multiple pregnancies, but there are few studies on effects of antenatal corticosteroids focussing exclusively on multiple gestations. Steroids are potent drugs with many unwanted effects. When given appropriately, they improve outcome. If not, then side effects, such as dose-dependent impaired foetal length and head circumference, impaired placental growth, brain apoptosis, and increased infection risk, may prevail. Long-term follow-up of children from trials conducted in the 1970s has been reassuring; however, steroids given after 34 weeks are associated with impaired outcome. Recent data from Finland raise concerns that any prenatal steroid has a negative effect on neurological, cognitive, and behavioural disorders, especially for infants who are born at term [31]. Although these data were obtained from within sib-pair comparisons and logistic regression, they may be biased by the occurrence of preterm contractions, which, in itself, may be a risk factor for neurodevelopmental deficits [32].

Steroids should only be given to women who really are going to deliver preterm. This continues to be a challenge since 40–50% of women receiving steroids deliver at term [27]. Unnecessary use of steroids might be reduced by accurate dating of duration of gestation, preterm birth risk assessment, restriction of repeated courses to a single course before 32 weeks, avoidance of steroids in women at risk of late preterm delivery, and by avoidance of unnecessary early elective CS. The current antenatal steroid dosage appears to be high, and the release of betamethasone acetate proceeds slowly for several days [33]. However, a recent RCT from France, in which a single betamethasone injection was compared to two injections 24 h apart (normal care), showed a 2.5 percent reduced need for surfactant in the full betamethasone arm but no between-group differences in rates of mortality, or other important outcomes [34]. Maternal BMI might be a confounder, and further studies are needed. The same holds for studies in early foetal growth restriction, in which steroids are widely used without any randomised studies indicating their effectiveness.

1. Mothers at high risk of preterm birth <28–30 weeks of gestation should be transferred to perinatal centres with experience in management of RDS (B1).
2. In women with a singleton pregnancy and a short cervix in mid-pregnancy or previous preterm birth, vaginal progesterone treatment should be used to increase gestational age at delivery and reduce perinatal mortality and morbidity (A1).
3. In women with symptoms of preterm labour, cervical length and accurate biomarker measurements should be considered to prevent unnecessary use of tocolytic drugs and/or antenatal steroids (B2).
4. Clinicians should offer a single course of prenatal corticosteroids to all women at high risk of preterm delivery, from when pregnancy is considered potentially viable up to 34 completed weeks of gestation, ideally at least 24 h before birth (A1).
5. A single repeat course of steroids may be given in threatened preterm birth before 32 weeks of gestation if the first course was administered at least 1–2 weeks earlier (A2).
6. MgSO₄ should be administered to women with imminent delivery before 32 weeks of gestation (A1).
7. Clinicians should consider short-term use of tocolytic drugs in very preterm pregnancies to allow completion of a course of prenatal corticosteroids and/or in utero transfer to a perinatal centre (B1).

Birth is defined as when the foetus is completely expelled from the mother, and this is when timings should start [35]. Personnel attending birth should know how to identify infants who require urgent airway management and lung inflation in the first minutes after birth in order to establish gas exchange and restore cardiac output. European Resuscitation Guidelines [36] cover protocols for when and how to intervene in infants who are born in poor condition secondary to hypoxia, with emphasis on airway opening and aeration of the lungs using positive pressure. A separate approach is needed for most preterm babies at risk of RDS as they are not asphyxiated and with time will try to breathe on their own [37], and supporting normal transition with more gentle interventions is preferable.

The timing of umbilical cord clamping is an important first step. Deferring cord clamping (DCC), allowing time for a placental transfusion, and establishing lung aeration before clamping will lead to a better haemodynamic transition. Avoiding immediate cord clamping in preterm infants has been recommended since 2010, and recently, it is clear that DCC of 30–60 s will reduce both in-hospital mortality [38] and the combined outcome of death or major disability at 2 years [39]. Umbilical cord milking was recommended as an alternative where DCC is not possible. Recent systematic reviews suggest equivalence in terms of haemodynamic benefits and overall outcomes [40]; however, one randomised trial was stopped early because of an excess of severe intraventricular haemorrhage in the subgroup of infants below 28 weeks of gestation [41]. Stabilising preterm babies on specially adapted resuscitation tables that allow optimal thermal care and airway management with the umbilical cord intact is also feasible [42], resulting in more rapid establishment of airway support and longer duration of DCC without needing to move to a separate overhead warmer. However, it is still not clear if this confers any overall benefits to most infants who will begin spontaneous breathing before the cord is clamped.

Repetitive stimulation such as stroking the back may be helpful in terms of establishing regular respirations with improved saturations observed in the first minutes after birth [43]. Early caffeine therapy also might improve respiratory effort [44], though further studies are needed before firm recommendations can be made [45].

For spontaneously breathing preterm infants, CPAP initiation rather than intubation will reduce lung injury and BPD [46]. Traditionally, this has been managed using a face mask and a CPAP level of around 5–6 cm H₂O; however, there is no strong evidence to recommend any particular level of pressure [47]. Routine sustained inflation of the lungs at birth should also not be performed as there is no evidence of benefit but evidence of harm in those <28 weeks [48]. T-piece devices allowing careful control of peak inspiratory pressures and PEEP are considered better than self-inflating bags. The interface between the CPAP device and the baby may also be important. Face mask application on its own may be sufficient to induce apnoea via the trigemino-cardiac reflex in spontaneously breathing infants [49]. Nasal interfaces offer an alternative method for CPAP provision at birth, but to date, no strong evidence exists that simply switching interface offers any clinical advantages [50]. Recently, a newly designed variable flow nasal prong CPAP delivery system reduced intubation requirements compared to standard T-Piece resuscitation with mask [51]. There is an urgent need for further work on improved interface design and strategies to provide early respiratory support to very preterm infants.

Heating and humidification of gases used for stabilisation is ideal in terms of preventing heat loss [52], but servo-controlled temperature regulation immediately after birth does not appear to confer any advantage [53]. Using plastic wraps and caps under radiant warmers for preterm babies <32 weeks will reduce hypothermia and result in less risk of IVH [52]; however, using these in combination with exothermic mattresses has the potential to cause overheating [54].

Significantly improved outcomes are found in newborn infants <32 weeks of gestation if SpO₂ reaches 80–85% within 5 min [55]. Further, bradycardia and especially prolonged bradycardia (HR <100 bpm more than 2 min) combined with insufficient SpO₂ (<80%) within 5 min increases the risk of death and IVH [56]. Monitoring infants' well-being during transition consists of assessment of adequate heart rate and saturations that are improving in line with normal values, increasing from

60% to 90% over the first 10 min after birth. It may take up to a minute to have reliable pulse oximetry readings for HR and SpO₂. Heart rate can be rapidly counted by auscultation, which is not as accurate as oximetry or ECG [57]; however, it is not clear whether rapid ECG-derived HR signal confers any meaningful clinical benefit [58]. Caregivers are quite capable of determining when HR <60 or above 100 bpm which is all that is needed [59]. Respiratory function monitoring with flow sensors can also provide information during stabilisation that can identify leaks, airway obstruction, and tidal volumes graphically. A recent meta-analysis showed a decrease in IVH when respiratory function monitoring was used, but more research is needed before it can be routinely recommended [60].

Blended air/oxygen should be available. For term babies, resuscitation starting in air is best, but for preterm babies <32 weeks, it is still unclear what the ideal starting oxygen level should be, with no difference in major outcomes in randomised trials [61]. Prolonged bradycardia and hypoxia can occur in the smallest infants started in air, so the consensus is that starting with FiO₂ around 0.30 for babies less than 29 weeks of gestation will give the best balance between avoiding hypoxaemia and causing oxidative stress [62]. A recent study has shown that starting with FiO₂ 1.0 with careful titration was more successful in reducing risk of hypoxaemia, without increasing risk of hyperoxaemia, when compared to starting with FiO₂ 0.30, and reducing hypoxaemia increased breathing effort [63]. Once transition has occurred and the infant is stable on CPAP, some centres would offer very early rescue surfactant to the smallest infants using the LISA technique in order to maximise the chance of avoiding MV [64].

When infants remain apnoeic and bradycardic, they need intubation for stabilisation, but this is in a minority of cases. Unfortunately, with increased use of non-invasive support, intubation skills are diminishing [65]. Regular simulation training with mannequins [66] and the use of video laryngoscopy for supervised intubations may help [67]. Delivery room intubations are usually indicated in infants born between 22 and 24 weeks and these or emergency intubations are usually performed without sedation [68]. If intubation is required, the correct placement of the endotracheal tube can be quickly verified by auscultation and by using a colourimetric CO₂ detection device. Low tidal volume or HFOV and early surfactant administration prior to radiographic confirmation of RDS is now the recommended practice, based on observational studies [69].

1. If clinical condition allows, defer clamping the umbilical cord for at least 60 s (A1). Only when DCC is not feasible, consider umbilical cord milking in infants with GA >28 weeks (B2)

2. T-piece devices should be used rather than bag and mask (B1)

3. Spontaneously breathing preterm infants should be stabilised using CPAP (A1). If apnoeic or bradycardic, start giving ventilation breaths. Expert consensus is to start with CPAP pressure at least 6 cm H₂O and peak inspiratory pressures 20–25 cm H₂O (D2)

4. Oxygen for resuscitation should be controlled using a blender. Use an initial FiO₂ of 0.30 for babies <28 weeks of gestation and 0.21–0.30 for those 28–31 weeks, 0.21 for 32 weeks of gestation and above. FiO₂ adjustments up or down should be guided by pulse oximetry (B2). SpO₂ of 80% or more (and heart rate >100/min) should be achieved within 5 min (C2).

5. Intubation should be reserved for babies not responding to positive pressure ventilation via face mask or nasal prongs (A1).

6. Plastic bags or occlusive wrapping under radiant warmers and humidified gas should be used during stabilisation for babies <32 weeks of gestation to reduce the risk of hypothermia. Hyperthermia should also be avoided (A1).

Surfactant therapy improves survival and reduces pneumothorax and therefore plays an essential role in management of RDS. Prior to 2013, prophylactic surfactant was recommended for the smallest babies as it improved survival in clinical trials from the pre-early CPAP era. Intratracheal surfactant administration requires skill and has the potential to cause harm, particularly when ventilating without controlling tidal volumes. Early initiation of CPAP may avoid the harmful effects of intubation and MV during the transitional phase, and since 2013, recommendations have been to only use surfactant in infants showing clinical signs of RDS. The overall aim is to avoid MV if possible while endeavouring to give surfactant as early as possible in the course of RDS, preferably using LISA methods.

Surfactant must be delivered directly to the trachea, and in most of the early trials, it was given as a bolus through an endotracheal tube, distributed by IPPV followed by a period of weaning ventilation. The IN-SUR-E technique, involving surfactant bolus administration followed by brief bag ventilation and rapid extubation without ongoing ventilation, seemed to reduce lung injury [70]. The accepted best method is to use a thin catheter for surfactant administration and avoid “bagging” completely, allowing the infant to maintain spontaneous breathing on CPAP while surfactant is gradually instilled in small aliquots. This method, known as less invasive surfactant administration (LISA) or minimally invasive surfactant administration, results in less need for MV and a reduction in the combined outcome of death or BPD as well as reduction in IVH in head-to-head comparisons with IN-SUR-E at identical treatment thresholds [71]. However, meta-analyses of multiple, individually small, non-blinded, underpowered studies may lead to over-estimating the benefits of LISA [72]. The largest study (OPTIMIST) randomised 485 babies of 25–28 weeks with blinding of the intervention: LISA surfactant versus sham procedure at FiO₂ threshold 30%. Although there was no significant difference in the primary outcome of death or BPD, there was a significant reduction in BPD in survivors favouring the treated infants (37% vs. 45%) [73]. However, it is unclear if any differences can be attributed solely to the LISA method, as earlier compared to later surfactant in RDS is already known to be beneficial, and two-thirds of control infants received surfactant [73]. The LISA technique has been widely adapted in many parts of Europe and in large cohort studies there are better clinical outcomes [74]. LISA prophylaxis is also used for the smallest infants in some centres, although the benefits are still being assessed in clinical trials, and there are concerns about negative effects related to laryngoscopy including destabilisation that inevitably occurs during surfactant administration. A high level of competence for the LISA procedure, rescue intubation, and CPAP application is required [75]. Two-year follow-up from one of the larger randomised trials also gives reassurance that the LISA technique is safe [76]. Early rescue with LISA also has potential to reduce overall costs of care [77].

Laryngoscopy for LISA surfactant is undoubtedly uncomfortable, but there is more chance of apnoeic episodes post-procedure requiring PPV if sedation is used [78]. In practice, the ease of the procedure seems unaffected whether opiates, oral sucrose, or no sedation is used [79]. Further clinical trials are underway to assess benefits and risks of sedation for LISA surfactant (NCT05065424). Alternative methods of getting adequate surfactant doses into the lung in a gentler way would be ideal. Laryngeal masks can be used to administer surfactant in babies [80]. A recent study confirmed non-inferiority to IN-SUR-E in preterm babies as low as 800 g, probably related to sedation protocols for endotracheal tube placement [81].

Modern nebulisers are capable of aerosolising surfactant, but to date, studies on nebulisation have not convincingly shown any meaningful improvement in smaller infants who should benefit most [82]. Pharyngeal deposition of surfactant at birth does not result in any clinical improvements [83].

If intubation is deemed necessary as part of stabilisation for preterm infants, then surfactant should be given to promote early extubation [84]. Most preterm infants will transition successfully on CPAP, but those with RDS will develop progressively worsening lung disease, clinically presenting as increased work of breathing, sternal recession, and increasing oxygen requirements to maintain normal saturations. Following the natural course of RDS, spontaneous recovery usually begins after 48–72 h, and infants with milder disease may manage without surfactant, thereby avoiding the discomfort of laryngoscopy and potential deleterious effects of intubation. Early trials showed that

surfactant given earlier in the course of disease works better than later in terms of reducing air leaks in babies ventilated for RDS [84] and avoiding MV if the IN-SUR-E technique is used [85]. This creates a dilemma for neonatologists as at present RDS severity is determined clinically, using a combination of FiO₂ requirements, coupled with judgement of work of breathing and other signs of respiratory distress alongside the degree of lung aeration on chest radiograph (or ultrasound), all of which can be influenced by CPAP. Ideally, predicting surfactant deficiency before the infant has deteriorated would enable earlier surfactant therapy of infants on CPAP and is likely to result in less need for MV and improved outcomes. Our previous recommendation to use FiO₂ > 0.30 as the threshold for surfactant treatment was based on observations of CPAP failure rates according to early postnatal oxygen requirements and is supported by more recent data [86]. In these studies, FiO₂ at 2 h of life was used to predict later CPAP failure, which was defined as oxygen requirement of 50–60%. In a newer similar study, CPAP failure was defined as oxygen requirement of 30% and thus optimal prediction was obtained at a 2-h FiO₂ as low as 23% [87]. As RDS is typically progressive over the first days of life, it is no surprise that FiO₂ cut-off for surfactant administration should be age specific. Furthermore, the use of early nasal ventilation and the knowledge that simply increasing mean airway pressure is likely to lower FiO₂ requirements, even in surfactant-deficient infants, contribute to the debate of optimal FiO₂ cut-off [88]. Lung ultrasound, with appropriate training, may offer an alternative way of diagnosing RDS at an earlier stage, without apparently resulting in more infants overall being treated [89]. Rapid bedside testing for surfactant components in gastric aspirate is also now available, and clinical trials of this new point-of-care test to determine surfactant need at birth are underway [90].

The dilemma as to whether to treat late-preterm and early-term infants with RDS with surfactant is being addressed in the SURFON Trial (<https://www.npeu.ox.ac.uk/surfon>). The current evidence for more mature infants with signs of RDS indicates a potentially decreased risk of mortality, air leaks, persistent pulmonary hypertension, and duration of respiratory support. However, due to heterogeneity of data, there is currently not enough evidence to make any recommendations [91].

More than one dose of surfactant may be needed. Many infants can continue on NIV even when surfactant is required. If poractant alfa is used, need for re-dosing can be minimised by using a larger initial dose of 200 mg/kg [92]. For other surfactants, such data are not available.

Three natural (animal derived) surfactants are currently available in Europe. Beractant (Survanta) at recommended dose of 100 mg/kg requires surfactant dose volume of 4 mL/kg. Bovactant (Alveofact) at recommended dose of 50 mg/kg requires volume of 1.2 mL/kg. Poractant alfa (Curosurf) at recommended dose of 100–200 mg/kg requires dose volume of 1.25–2.5 mL/kg. Head-to-head trials show similar efficacy among surfactants when used in similar doses; however, there is a survival advantage when poractant alfa at the higher dose of 200 mg/kg is compared to 100 mg/kg of poractant alfa or beractant [93]. New synthetic surfactants with surfactant protein analogues have shown promise in clinical trials, potentially negating the need for animals in surfactant production, but these are not yet commercially available [94]. Using surfactant with added budesonide may also reduce BPD [95]. Further studies are underway, and we should await the outcomes of these before recommendations are made (<https://www.plusstrial.org>).

1. If a preterm baby <30 weeks of gestation requires intubation for stabilisation, they should be given surfactant (A2).
2. Babies with RDS needing treatment should be given an animal-derived surfactant preparation (A1).
3. LISA is the preferred method of surfactant administration for spontaneously breathing babies on CPAP (A1).
4. Laryngeal mask surfactant may be used for more mature infants >1.0 kg (B2).

5. An initial dose of 200 mg/kg of poractant alfa is better than 100 mg/kg of poractant alfa or 100 mg/kg beractant for rescue therapy (A1).
6. Rescue surfactant should be given early in the course of the disease (A1). Suggested protocol would be to treat worsening babies with RDS when $\text{FiO}_2 > 0.30$ on CPAP pressure ≥ 6 cm H₂O or if lung ultrasound suggests surfactant need (B2).
7. A second and occasionally a third dose of surfactant should be given if there is ongoing evidence of RDS such as persistent high oxygen requirement and other problems have been excluded (A1).

There are no relevant changes since 2019 in terms of refining previous recommendations for oxygen saturation targeting based on data from the NeOProm Collaboration [96]. Targeting lower saturations (85–89% vs. 91–95%) reduces risk of severe retinopathy of prematurity (ROP) but at expense of increasing mortality (RR 1.17; 95% CI: 1.04–1.31) and NEC. Recommendations therefore remain the same, targeting saturations between 90 and 94% by setting alarm limits between 89 and 95%, although ideal oxygen saturation targets are still unknown, particularly for preterm babies above 30 weeks [97]. There are no scientific data supporting the choice of alarm limits. We argue for tight alarm limits to prevent fluctuations in oxygenation and avoid hypoxaemia and or hyperoxaemia. Recent publications have emphasised an increased incidence of ROP associated with higher oxygen saturation ranges in the NICU [98]. Therefore, it is recommended that there be stringent surveillance for prevention and early treatment of ROP, especially in preterm infants at the lowest gestational ages. Recently, a Swedish study confirmed that lowering saturation targets is associated with less ROP but greater risk of NEC and higher mortality [99].

Approximately 20% of infants with BPD will develop pulmonary hypertension. The optimal oxygen saturation targeting strategy to prevent and/or support extremely preterm infants with pulmonary hypertension remains unclear. However, a 50% reduction in BPD-associated pulmonary hypertension was observed in babies <29 weeks of gestation after oxygen saturation targets were increased from 88–92% to 90–95%, supporting use of higher saturation targets in these infants [100].

Reliability of servo-controlled algorithms for keeping oxygen saturations within defined ranges has been tested in the delivery room [101] as well as in MV [102] and NIV neonates [103]. Automated oxygen control significantly increases the time within the intended range, thus potentially reducing nursing workload. However, long-term clinical benefits are yet to be determined.

1. In preterm babies receiving oxygen, the saturation target should be between 90 and 94% (B2).
2. Alarm limits should be set to 89% and 95% (D2)
3. Protocols for screening and treating preterm babies for ROP should be in place (A1)

Preterm infants should be managed without MV where possible and if needed, time on MV should be minimised. CPAP has been successfully used for >50 years for stabilising preterm infants, in both high- and middle-to-low-income settings [104]. CPAP improves lung volume, especially functional residual capacity. The increased positive distending airway pressure improves oxygenation, decreases apnoea, and reduces the work of breathing. Thus, CPAP is recommended as the first choice for primary and secondary respiratory support [105 , 106 , 107]. However, alternative modes of NIV are increasingly being tested in clinical trials against CPAP as the gold standard.

CPAP involves delivering gas, ideally heated and humidified, with a measurable and controllable pressure which is transmitted using an interface such as short soft nasal prongs or mask, connected tightly to the baby's face creating a seal. CPAP pressures are typically set between 5

and 9 cm H₂O. Increasing airway pressure provides several benefits including splinting the upper airway, maintaining lung expansion, and preventing end-expiratory alveolar collapse. Other benefits include reduced apnoea rates, improved tidal volumes, higher functional residual capacity, and reduced work of breathing. Higher pressures improve oxygenation but potentially increase risk of air leaks. An underwater seal or “bubble CPAP,” to generate the pressure, causes small fluctuations around the set pressure which some believe offers the additional advantage of improved CO₂ washout [108]. When weaning babies from CPAP, a gradual reduction in pressure rather than sudden cessation of CPAP results in greater likelihood of success [109].

Using a flow driver to generate CPAP has the theoretical advantage of offloading expiratory work of breathing, although no important clinical differences have been shown in clinical trials among various CPAP devices. The simplicity of bubble CPAP systems allows their use in low-income settings with some evidence of benefit over free-flowing oxygen [104]. Leaks between the interface and nose are common with both nasal prongs and masks but somewhat less with prongs [110]. All CPAP interfaces carry risk of facial distortion and nasal trauma [111].

Bi-level CPAP, Duo-PAP, or BIPAP are variants between CPAP and IPPV that use low pressure differences between inspiratory and expiratory phases at PIPs of 9–11 cm H₂O at rates of around 20–40 per minute with long inspiratory times of up to 1.0 s. There is no evidence that BIPAP confers any advantage over CPAP, and any clinical differences may simply reflect a higher overall mean airway pressure [112]. Modern ventilators provide NIPPV using pressures similar to those used for invasive MV. Challenges of NIPPV relate to pressure delivery through a non-sealed system, which is limited by leak at the nasal interface and the infant's tolerance to gas inflation of the stomach. Ventilator inflations can be synchronised with the infant's breathing by using either an abdominal capsule or in-line sensors. Synchronisation of nasal ventilation further improves respiratory stability [113]. Recent systematic reviews comparing different modes of NIV for primary respiratory support or post-extubation concluded that synchronised NIPPV was the most effective, decreasing the need for MV, or re-ventilation, in preterm infants [114 , 115].

Supraglottic application of nasal HFOV (nHFOV) is used in some centres in Europe [116] and is the subject of ongoing research [117]. The oscillations are apparently transmitted all the way down to the lungs [118]. Regional ventilation may be similar between nHFOV and CPAP, while end-expiratory lung volume may be higher and aeration homogeneity slightly improved during nHFOV [119]. To date, four RCTs have compared nHFOV to CPAP, and a systematic review suggests that nHFOV decreases intubation rates when compared to CPAP [118]. However, there is lack of clarity in the methodology of some of the studies included as to how nHFOV was performed, making it difficult for studies to be replicated and for firm recommendations to be made.

Heated humidified high flow nasal cannulae (HFNC) are being increasingly used as an alternative to CPAP [120]. With HFNC, heated/humidified gas is delivered to the nostrils with nasal catheters that are specifically designed not to occlude the nostrils. Typically, flows of between 2 and 8 L/min are used, with weaning of flow rate determined clinically by FiO₂ remaining low and a judgement of work of breathing [121]. Although HFNC undoubtedly generates some pharyngeal distending pressure, this is not measured, and the primary mode of action is likely related to gas conditioning and nasopharyngeal dead space CO₂ washout [121]. In clinical trials, HFNC is broadly observed as equivalent to CPAP for babies >28 weeks coming off MV, with greater ease of use and less nasal trauma [122], although there is less evidence for smaller babies. In a large-scale non-inferiority RCT, HFNC more often resulted in treatment failure compared to CPAP, but the need for MV was similar [123], and inferiority related to this predefined primary outcome should not necessarily be equated with futility [124]. Clinicians from centres familiar with both HFNC and CPAP argue that with growing experience, HFNC can be used as initial support strategy, even in the smallest babies, and this is supported by recent systematic reviews [125 , 126].

Acknowledging the many positive attributes of HFNC, including less nasal trauma, reduced pneumothorax, greater patient satisfaction, and parent and nursing staff preference, a more recent meta-analysis of HFNC trials recommends HFNC use as a first-line option for respiratory support in centres capable of offering CPAP and/or NIPPV as a backup [126]. There will likely be further

refinements of NIV over the coming years. Better synchronisation with the baby's own breathing efforts may be a central element of modern ventilatory support. This could potentially be achieved by using the neurally adjusted ventilator assistance technology [127]. A recent small RCT suggests NIV-NAVA may be effective in preventing extubation failure in preterm infants, with lower PIP following extubation; however, the study was not powered to look at important clinical outcomes [128]. Larger clinical trials of NAVA and other newer modes of support are urgently needed.

1. CPAP or (s)NIPPV should be started from birth in all babies at risk of RDS, such as those <30 weeks of gestation who do not need intubation for stabilisation (A1).
2. NIV with early rescue surfactant by LISA technique is considered optimal management for babies with RDS (A1).
3. The system delivering CPAP is of little importance; however, the interface should be short binasal prongs or mask with a starting pressure of about 6–8 cm H₂O (A2). Ability to escalate to NIPPV will reduce the need for invasive MV in some infants (A1).
4. BIPAP devices confer no advantage over CPAP alone (A2). However, synchronised NIPPV, if delivered through a ventilator, can reduce need for ventilation or need for re-ventilation following extubation and may reduce BPD (A2).
5. HFNC can be used as an alternative to CPAP for some babies, with the advantage of less nasal trauma, provided centres have access to CPAP or NIPPV for those failing this mode (B2).

Despite best efforts to maintain as many preterm babies as possible on NIV, around half of babies <28 weeks will require MV and those that do have worse outcomes [129]. In addition, around half of infants <28 weeks will also fail their first attempt at extubation and they too have worse outcomes [130]. It is important that those managing infants with RDS understand the principles of MV to minimise the risk of iatrogenic lung injury. The aim of MV is to provide “acceptable” blood gases by ventilating at optimal lung volumes (open lung concept) while avoiding over-distension and atelectasis. Pulmonary over-distension increases risk of air leaks and pulmonary interstitial emphysema, while ventilating at sub-optimally low pressures may cause atelectasis and repeated pulmonary shear stress, which in turn can generate inflammation and lung injury.

Modern ventilators have flow sensors that measure the volume of gas entering and leaving the endotracheal tube to help synchronise MV with the infant's own breathing efforts and may be used to limit the support provided to prevent lung over-distension. Volume-targeted ventilation (VTV) allows real-time weaning of pressure as lung compliance improves and results in less time on ventilation, fewer air leaks, and less BPD [131]. Setting an initial tidal volume of around 5 mL/kg with a maximum PIP at a safe level, around 25–30 cm H₂O, with adjustments in initial tidal volumes according to judgement of work of breathing and blood gas assessment is usually straightforward but may fail if the endotracheal tube leak is high. Adjusting PEEP to maintain an open lung is judged by finding a point where FiO₂ is at its lowest with haemodynamic stability and acceptable blood gases. Required tidal volumes vary around 5–7 mL/kg; the range tends to increase with increasing postnatal age [132]. Ventilation modes supporting every spontaneous breath rather than synchronised IMV makes sense, although if volume targeting is not possible, it may be safer to use synchronised IMV where the ventilation rate is clinician controlled [133]. Volume targeting can reduce hypocarbia in even the smallest infants [134]. Supporting the infants' own respiratory efforts with modes where both inspiration and expiration are synchronised, such as pressure support or NAVA, can improve patient comfort and facilitate weaning. However, to date, no differences have been shown in longer term clinical outcomes [135 , 136].

HFOV is a ventilation strategy that facilitates gas exchange by very small gas volume delivery at fast rates to an optimally inflated lung, using a continuous distending pressure (CDP).

Meta-analysis of studies comparing HFOV to conventional ventilation shows a modest reduction in BPD; however, there is a paucity of data from contemporary trials, comparing HFOV to VTV [137]. Determining the optimal distending pressure clinically involves finding the pressure at which oxygenation deteriorates during a stepwise reduction from full lung inflation and aiming for 1–2 cm H₂O above this, bearing in mind that as compliance improves, the lung may become over-distended if the set pressure is not weaned [138]. Volume targeting in HFOV reduces CO₂ variability [139] and allows effective ventilation with very small tidal volumes, which may be lung protective. Whatever ventilation system is used within an individual unit, it is important that all staff should be familiar with it.

Inhaled nitric oxide (INO) is a proven therapy for hypoxaemic respiratory failure in term babies with pulmonary hypertension. Although there is no significant effect of INO on mortality or BPD in preterm infants <34 weeks of gestational age [140], it is still often used on a physiological rationale during hypoxic respiratory failure. INO should not be used as a panacea for infants with poor oxygenation since INO is a toxic oxidant. However, for a small subgroup of preterm infants, with a history of mid-trimester oligohydramnios, birth asphyxia, and documented pulmonary hypertension with severe respiratory distress, brief NO treatment can result in rapid improvement in oxygenation, allowing ventilator settings to be reduced to safer levels [141].

At initiation of MV, lung recruitment may be used to optimise PEEP, but there is little evidence it influences outcome [142]; however, lung recruitment before surfactant administration may lead to successful early extubation [143]. Once stabilised on MV and with demonstrable spontaneous breathing effort, clinicians should immediately start planning for weaning to NIV [144]. Some infants require a very short period of ventilation, particularly those with RDS following surfactant therapy, and early extubation of even the smallest babies who achieve low ventilator settings should be encouraged. Infant's size, absence of growth restriction, oxygen requirement, and blood gases can all help determine extubation success [130]. Delaying extubation does not improve the chance of success [145]. Trials of endotracheal tube CPAP to predict extubation readiness are not that helpful [146]. Mathematical models for predicting extubation success may be useful, but their potential to improve outcomes has yet to be evaluated [147]. Extubation is possible from when MAP reaches about 7–8 cm H₂O on conventional ventilation or a CDP of 8–9 cm H₂O on HFOV. Extubating to a relatively higher CPAP pressure of 7–9 cm H₂O or NIPPV will improve chance of success [148], although at present, there are no data to support any particular CPAP level in terms of influencing longer term outcomes [47].

Methylxanthines are respiratory stimulants, and caffeine therapy is now a well-established aspect of newborn respiratory care. The Caffeine for Apnea of Prematurity (CAP) study confirmed that caffeine in the standard dose of 20 mg/kg loading with 5–10 mg/kg day maintenance for infants <1,251 g coming off MV, or being treated for apnoea, resulted in less need for respiratory support, subsequently less BPD, and long-term follow-up also showing improved neurodevelopmental outcomes [149]. Subgroup analysis from the CAP trial showed better outcomes with earlier treatment [150]. Caffeine prophylaxis has become widespread based on cohort studies, despite the risk of bias, since earlier treatment is associated with better outcomes [150, 151]. Randomised trials of caffeine prophylaxis for extremely preterm infants are scarce and show conflicting results [152, 153], and further studies combining caffeine prophylaxis with LISA are currently underway. Higher doses may further improve respiratory outcomes but are associated with risk of adverse effects such as seizures or cerebellar haemorrhage. Gradual increase in dosing from 5 towards 8 mg/kg/day over several weeks may give the best chance of maintaining therapeutic effect [154].

The concept of facilitating earlier extubation by tolerating mild hypercapnia is long-standing [155]. Recent systematic review suggests the safest range for CO₂ is around 5–7 kPa, with hypocapnia in preterm infants being associated with increased risk of periventricular leukomalacia and severe hypercapnia linked with IVH, NEC, BPD, and ROP [156]. Permissive hypercapnia will potentially allow reduced tidal volumes and facilitate extubation, though there is no convincing evidence that it reduces BPD. The optimal CO₂ target remains to be determined; however, the consensus view is

that tolerating modest degrees of hypercarbia is reasonable, provided the pH is acceptable.

Despite best efforts, some infants are difficult to wean from MV with an apparent cycle of MV-induced lung inflammation and increased risk of BPD. Systemic corticosteroids have a role in breaking this cycle to facilitate extubation and improve outcomes [157 , 158]. However, steroids are powerful drugs, increasing risk of gastrointestinal perforations, and have potential to increase risk of long-term neurological problems, particularly if used within the first week of life. Meta-regression analysis suggests that the greater the risk of BPD, the more the balance tips in favour of using steroids to improve overall long-term outcomes [159]. The lower dose dexamethasone regimen described in the DART trial seems to get the best balance of clinical effectiveness with minimising risk of longer term side effects [160 , 161]. Low-dose prophylactic hydrocortisone for 10–15 days from birth also improves chances of survival without BPD and reduces need for PDA treatment [162]. Concerns about effects on brain growth in observational cohorts exposed to postnatal hydrocortisone can be explained by the infants being sicker, and ventilated for longer, rather than a direct effect of hydrocortisone per se [163]. Some centres have already adopted routine early hydrocortisone supplementation to improve perinatal outcomes. However, early routine hydrocortisone may have negative interaction with potential high levels of endogenous cortisol (if not measured), which may increase the risk of severe IVH and spontaneous intestinal perforation [164]. Hydrocortisone prophylaxis seems promising, but more work is required before it is routinely adopted for all preterm infants, especially those below 26 weeks of gestation [165]. Prophylactic inhaled corticosteroids would be a logical alternative, and there is evidence of a reduction in BPD if inhaled budesonide or fluticasone is started from birth [166 , 167]. The largest study of inhaled budesonide showed inexplicable higher mortality in the inhaled steroid-treated group, thereby prompting caution in recommending routine inhaled steroid prophylaxis [168 , 169].

Preterm babies can clearly experience pain and discomfort. There is a balance between appropriate analgesia and the negative effects of sedation, particularly when there is an emphasis on minimising duration of MV. Routine sedation for ventilated infants is not recommended [170]. Delivery room endotracheal intubations are often emergencies and not usually performed under sedation [68]. However, for elective intubations in the NICU, sedation with an opioid and muscle relaxant results in greater intubation success on the first attempt [171]. Sedation for LISA is discussed in the surfactant section.

1. MV should be used in babies with RDS when other methods of respiratory support have failed (A1). Duration of MV should be minimised (B2).
2. Lung-protective modes such as VTV or high-frequency oscillation ventilation should be the first choice for babies with RDS who require MV (A1).
3. When weaning from MV, it is reasonable to tolerate a modest degree of hypercarbia, provided the pH remains above 7.22 (B2). Avoid $p\text{CO}_2 < 4.7$ kPa (35 mm Hg) when on MV to reduce brain injury (C1).
5. INO in preterm babies should be limited to a therapeutic trial for those in whom there is documented pulmonary hypertension with severe respiratory distress and stopped if there is no response (D2).
4. Caffeine (20 mg/kg loading, 5–10 mg/kg maintenance) should be used to facilitate weaning from MV (A1). Early caffeine can be considered for babies at high risk of needing MV such as preterm babies on NIV (C1).
5. A short tapering course of low-dose dexamethasone should be considered to facilitate extubation in babies who remain on MV after 1–2 weeks (A2).

6. Opioids should be used selectively when indicated by clinical judgement and evaluation of pain indicators (D1). The routine use of morphine or midazolam infusions in ventilated preterm infants is not recommended (A1).

Monitoring physiological variables in preterm babies is an important part of quality care. Pulse oximetry from birth can help titrate oxygen. In the NICU, there should be access to continuous pulse oximetry and ECG monitoring and a means of measuring PaCO₂. Detection of exhaled CO₂ by colourimetric devices can confirm correct placement of endotracheal tubes. Continuous end-tidal CO₂ confirms ongoing correct tube placement as well as showing trends in gas exchange. Transcutaneous oxygen and CO₂ monitoring can give continuous information for trending, but readings can be affected by other conditions such as sepsis [172]. Arterial blood gases are the gold standard, and umbilical or peripheral arterial cannulation is necessary if regular blood gases or if continuous blood pressure monitoring is required. Methods of monitoring cerebral oxygenation by near-infrared spectroscopy are available to enable clinicians to detect and reverse cerebral hypoxia [173], although whether this improves outcomes is still to be tested in large clinical trials. Close monitoring of haematological values and electrolytes ideally using very small volumes of blood is essential. There should be access to portable ultrasound and round-the-clock access to radiology services, which are needed to confirm RDS diagnosis and ensure correct placement of tubes and lines.

Maintaining normal body temperature is an important quality measure as admission hypothermia is associated with worse outcomes, regardless of hospital performance [174]. In newborn preterm infants, immediate wrapping in a food-grade polythene bag or foil, placement under a radiant warmer, and humidification of gases are proven effective measures for reducing heat loss. After admission, babies should be managed in servo-controlled incubators, initially with relatively high humidity which can be reduced as skin integrity improves. Periods of skin-to-skin care are also an effective means of maintaining temperature and should be encouraged as they maximise bonding and improve growth and breastfeeding rates for VLBW infants [175].

Mothers are often treated with intrapartum antibiotic prophylaxis if they present in preterm labour to reduce risk of group B streptococcal infection in the infant [176]. Antibiotics are also frequently started in babies with RDS until sepsis has been excluded, and it is important to have policies in place to narrow the spectrum and minimise duration, as antibiotic overuse is associated with adverse effects such as increased risk of NEC [177]. Guidelines should be in place to only screen for sepsis when there are additional risk factors or signs of sepsis, and it is reasonable to withhold antibiotics in low-risk scenarios such as infants born by elective caesarean section. If antibiotics are started empirically, it should be possible to stop them within 36 h if there is no clinical or laboratory evidence of sepsis [178].

The smallest infants have very high initial transcutaneous water losses and water and sodium move from the interstitial to the intravascular compartments, making fluid balance challenging. Humidified incubators rather than overhead warmers help reduce insensible losses. Fluids are initiated at about 70–80 mL/kg/day and adjustments individualised according to fluid balance, weight change, and serum electrolyte levels. A modest early postnatal weight loss is normal. Regimens with more restricted fluids have better outcomes with reductions in PDA, NEC, and BPD [179]. Delaying introduction of sodium supplementation until beyond the third day or 5% weight loss will also improve outcome [180]. Parenteral nutrition should be started immediately as enteral feeding is initially limited. Early initiation of higher levels of parenteral amino acids results in less postnatal growth failure and an increase in positive protein balance [181]. At least 1.5 g/kg intravenous protein and 1–2 g/kg lipids should be started from day 1 and increased to a maximum of 3.5 g/kg amino acid [182 , 183]. For stable infants, a small amount (0.5–1 mL/kg/h) of breast milk can be started early to initiate enteral feeding [184]. There is no evidence of increased NEC with advancing feeds fairly rapidly up to 30 mL/kg/day in stable VLBW babies [185]. Mother's milk is the preferred option for initiation of feeding but if not available then pasteurised donor breast milk is better than formula for reducing risk of NEC but will result in slower postnatal growth [186].

1. Core temperature should be maintained between 36.5°C and 37.5°C at all times (C1).
2. Most babies should be started on intravenous fluids of 70–80 mL/kg/day in a humidified incubator, although some very immature babies may need more (C2). Fluids must be tailored individually according to serum sodium levels, urine output, and weight loss (D1).
3. Parenteral nutrition should be started from birth. Amino acids 1.5–2 g/kg/d should be started from day 1 and quickly built up to 2.5–3.5 g/kg/d (B2). Lipids 1–2 g/kg/d should be started from day 1 and quickly built up to 4.0 g/kg/day as tolerated (C2).
4. Enteral feeding with mother's milk should be started from the first day if the baby is hemodynamically stable (B2).
5. In infants with RDS, antibiotics should be used judiciously and stopped early when sepsis is ruled out (D1).

Hypotension and low systemic blood flow are associated with adverse outcomes, although thresholds for treating low blood pressure are unclear and very difficult to study [187]. Hypotension is associated with cerebral hypoxia, and the longer the hypoxia, the greater the risk of IVH; however, increasing blood pressure using dopamine may not change cerebral oxygenation [188]. Normal values are available showing lower blood pressure with decreasing gestation but increasing gradually over the first days and a wide variation at each gestational age [189]. Higher mean blood pressure after birth is achieved with antenatal steroid use, delayed cord clamping, and avoidance of MV. Neonatologist-performed functional echocardiography requires training but allows assessment of the cause of hypotension such as hypovolaemia, ductal shunting, or poor myocardial contractility [190]. Hypovolaemia is probably over-diagnosed, and administration of saline boluses is associated with poorer outcomes [191]. Dopamine is more effective than dobutamine at increasing blood pressure in hypotensive infants, although adrenaline may be a more rational choice in the setting of reduced ventricular function [192]. Hydrocortisone is also an effective inotrope and should be considered for extremely preterm infants who are at risk of low serum cortisol [193].

All infants start life with a patent (open) ductus arteriosus (PDA), and most will close spontaneously, but persistence of PDA and its potential adverse effects remain highest among the least mature infants. Hemodynamically significant PDA increases pulmonary oedema and decreases systemic cardiac output as the PVR gradually falls after birth. Although CDP reduces lung oedema and inotropic drugs can improve cardiac contractility, early closure of ductus remains desirable. PDA requiring medical closure is associated with increased risk of death, BPD, IVH, and NEC. Recent large cohort studies suggest that active early screening and treatment of PDA can reduce pulmonary haemorrhage and in-hospital mortality [194] and lower the risk of BPD [195]. Ibuprofen, indomethacin, or paracetamol induce closure of PDA, and differences in efficacy among the individual drugs or the administration route may be due to population variation [196 , 197 , 198]. Ibuprofen and particularly indomethacin increase risk of gastrointestinal perforation and bleeding and risk of renal insufficiency. Although paracetamol may cause hepatic and pulmonary toxicity due to oxidant injury, and antenatal exposure may predispose to neuro-psychiatric problems in early childhood, the few follow-up studies of infants receiving paracetamol soon after birth have failed to confirm significant adverse effects [199]. Routine treatment of preterm babies to promote PDA closure is not considered good practice [200]. Expectant management of PDA versus treatment is being explored in clinical trials [201] as well as early treatment with paracetamol. Surgical ligation has a place only if medical therapy has failed and the PDA is causing significant clinical problems [202].

Maintaining a reasonable Hb concentration is also important and late cord clamping contributes towards this goal. Randomised trials comparing targeting lower versus higher Hb concentrations (about 1–2 g/dL lower) show that targeting lower transfusion thresholds result in reduced need for blood transfusion without affecting hospital outcomes, and recent, major randomised controlled

trials found similar long-term outcomes [203 , 204]. The thresholds proposed in these guidelines therefore approximate the lower thresholds used in these trials [205].

1. Treatment of hypotension is recommended when there is evidence of poor tissue perfusion such as oliguria, acidosis, and poor capillary refill (C2). Treatment will depend on the cause.
2. When a decision is made to attempt pharmacologic closure of hemodynamically significant PDA, indomethacin, ibuprofen, or paracetamol can be used with a similar efficacy (A2). Paracetamol is preferred when there is thrombocytopaenia or concerns about renal function (B2).
3. Thresholds for red blood cell transfusion in infants can be set at 12 g/dL (HCT 36%) for those with severe cardiorespiratory disease, 11 g/dL (HCT 30%) for those who are oxygen dependent, and 7 g/dL (HCT 25%) for stable infants beyond 2 weeks of age (A2).

Therapy-resistant severe respiratory distress due to malformations, alveolar-capillary dysplasia, damaging mutations including SP-B, ABCA3, or TTF-1, or due to extreme structural immaturity is beyond the scope of these guidelines. On the other hand, surfactant therapy is reported to be useful in other serious situations where secondary surfactant inactivation occurs such as in pneumonia [206], pulmonary haemorrhage [207], or meconium aspiration syndrome [208]. Surfactant has also been trialled in preterm infants with evolving BPD who remain on MV at 2 weeks of age. Although there was no reduction in BPD at 36 weeks, surfactant-treated infants had fewer episodes of rehospitalisation over the first year of life [209]. Routine surfactant therapy is not recommended in infants with congenital diaphragmatic hernia [210].

Surfactant can be used for RDS complicated by congenital pneumonia (C2).

Surfactant therapy can improve oxygenation following pulmonary haemorrhage (C1).

Surfactant can improve oxygenation in infants with severe meconium aspiration syndrome (B2).

Henry L. Halliday, Christian P. Speer, and Charles C. Roehr in the past have been consultants to Chiesi Farmaceutici, Parma, the manufacturer of a leading animal-derived surfactant preparation used to treat RDS and a caffeine product for treatment of apnoea of prematurity. Virgilio Carnielli is a member of the Chiesi Farmaceutici Advisory Board. Henry Halliday and Christian Speer are joint chief editors of Neonatology .

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Bell EF Hintz SR Hansen NI Bann CM Wyckoff MH DeMauro SB Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Mortality, in-hospital morbidity, care practices, and 2-year outcomes for extremely preterm infants in the US, 2013-2018 JAMA 2022 Jan 18 327 (3) 248-263 35040888 10.1001/jama.2021.23580 PMC8767441 2 Watkins PL Dagle JM Bell EF Colaizy TT Outcomes at 18 to 22 months of corrected age for infants born at 22 to 25 weeks of gestation in a center practicing active management J Pediatr 2020 Feb 217 52-58 e1 31606151 10.1016/j.jpeds.2019.08.028 3 Haumont D Modi N Saugstad OD Antetere R NguyenBa C Turner M Evaluating preterm care across Europe using the eNewborn European Network database Pediatr Res 2020 Sep 88 (3) 484-495 31972855 10.1038/s41390-020-0769-x 4 Sweet D Bevilacqua G Carnielli V Greisen G Plavka R Saugstad OD European consensus guidelines on the management of neonatal respiratory distress syndrome J Perinat Med 2007 35 (3) 175-186 17480144 10.1515/JPM.2007.048 5 Sweet DG Carnielli V Greisen G Hallman M Ozek E Plavka R European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants: 2010 update Neonatology 2010 Jun 97 (4) 402-417 20551710 10.1159/000297773 6 Sweet DG Carnielli V Greisen G Hallman M Ozek E Plavka R European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants: 2013 update Neonatology 2013 103 (4) 353-368 23736015 10.1159/000349928 7 Sweet DG Carnielli V Greisen G Hallman M Ozek E Plavka R European consensus guidelines on the management of respiratory distress syndrome: 2016 update Neonatology 2017 111 (2) 107-125 27649091 10.1159/000448985 8 Sweet DG Carnielli V Greisen G Hallman M Ozek E Te Pas A European consensus guidelines on the management of respiratory distress syndrome: 2019 update Neonatology 2019 115 (4) 432-450 30974433 10.1159/000499361 PMC6604659 9 Guyatt GH Oxman AD Kunz R Falck-Ytter Y Vist GE Liberati A Going from evidence to recommendations BMJ 2008 May 10 336 (7652) 1049-1051 18467413 10.1136/bmj.39493.646875.AE PMC2376019 10 Diguisto C Foix L Helias L Morgan AS Ancel PY Kayem G Kaminski M Neonatal outcomes in extremely preterm newborns admitted to intensive care after no active antenatal management: a population-based cohort study J Pediatr 2018 Dec 203 150-155 30270165 10.1016/j.jpeds.2018.07.072 11 Duley L Meher S Hunter KE Seidler AL Askie LM Antiplatelet agents for preventing pre-eclampsia and its complications Cochrane Database Syst Rev 2019 Oct 30 2019 (10) CD004659 31684684 10.1002/14651858.CD004659.pub3 PMC6820858 12 EPPPIC Group Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials Lancet 2021 397 (10280) 1183-1194 33773630 10.1016/S0140-6736(21)00217-8 13 Norman JE Progesterone and preterm birth Int J Gynaecol Obstet 2020 Jul 150 (1) 24-30 32524598 10.1002/ijgo.13187 PMC8453855 14 Alfirevic Z Stampalija T Medley N Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy Cochrane Database Syst Rev 2017 Jun 6 6 (6) CD008991 28586127 10.1002/14651858.CD008991.pub3 PMC6481522 15 Middleton P Gomersall JC Gould JF Shepherd E Olsen SF Makrides M Omega-3 fatty acid addition during pregnancy Cochrane Database Syst Rev 2018 Nov 15 11 (11) CD003402 30480773 10.1002/14651858.CD003402.pub3 PMC6516961 16 Melchor JC Khalil A Wing D Schleussner E Surbek D Prediction of preterm delivery in symptomatic women using PAMG-1, fetal fibronectin and pHGFBP-1 tests: systematic review and meta-analysis Ultrasound Obstet Gynecol 2018 Oct 52 (4) 442-451 29920825 10.1002/uog.19119 17 Marlow N Bennett C Draper ES Hennessy EM Morgan AS Costeloe KL Perinatal outcomes for extremely preterm babies in relation to place of birth in England: the EPICure 2 study Arch Dis Child Fetal Neonatal Ed 2014 99 (3) F181-8 24604108 10.1136/archdischild-2013-305555 PMC3995269 18 Kenyon S Boulvain M Neilson JP Antibiotics for preterm rupture of membranes Cochrane Database Syst Rev 2013 Dec 2 (12) CD001058 24297389 10.1002/14651858.CD001058.pub3 PMC11297390 19 Wolf HT Huusom LD Henriksen TB Hegaard HK Brok J Pinborg A Magnesium sulphate for fetal neuroprotection at imminent risk for preterm delivery: a systematic review with meta-analysis and trial sequential analysis BJOG 2020 Sep 127 (10) 1180-1188 32237069 10.1111/1471-0528.16238 20 Haas DM Caldwell DM Kirkpatrick P McIntosh JJ Welton NJ Tocolytic therapy for preterm delivery: systematic review and network meta-analysis BMJ 2012 Oct 9 345 e6226 23048010 10.1136/bmj.e6226 PMC4688428 21 Roberts D Brown J Medley N Dalziel SR Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth Cochrane Database Syst Rev 2017 Mar 21 3 (3)

CD004454 28321847 10.1002/14651858.CD004454.pub3 PMC6464568 22 Ehret DEY Edwards EM Greenberg LT Bernstein IM Buzas JS Soll RF Association of antenatal steroid exposure with survival among infants receiving postnatal life support at 22 to 25 Weeks' gestation JAMA Netw Open 2018 Oct 5 1 (6) e183235 30646235 10.1001/jamanetworkopen.2018.3235 PMC6324435 23 Cahill AG Kaimal AJ Kuller JA Turrentine MA ACOG Practice Advisory. Use of Antenatal Steroids at 22 weeks of gestation 24 Gyamfi-Bannerman C Thom EA Blackwell SC Tita AT Reddy UM Saade GR Antenatal betamethasone for women at risk for late preterm delivery N Engl J Med 2016 Apr 7 374 (14) 1311 1320 26842679 10.1056/NEJMoa1516783 PMC4823164 25 Gulersen M Gyamfi-Bannerman C Greenman M Lenchner E Rochelson B Bornstein E Time interval from late preterm antenatal corticosteroid administration to delivery and the impact on neonatal outcomes Am J Obstet Gynecol MFM 2021 Sep 3 (5) 100426 34153514 10.1016/j.ajogmf.2021.100426 26 Kamath-Rayne BD Rozance PJ Goldenberg RL Jobe AH Antenatal corticosteroids beyond 34 weeks gestation: what do we do now? Am J Obstet Gynecol 2016 Oct 215 (4) 423 430 27342043 10.1016/j.ajog.2016.06.023 27 Ninan K Liyanage SK Murphy KE Asztalos EV McDonald SD Evaluation of long-term outcomes associated with preterm exposure to antenatal corticosteroids: a systematic review and meta-analysis JAMA Pediatr 2022 Apr 11 176 (6) e220483 35404395 10.1001/jamapediatrics.2022.0483 PMC9002717 28 Norman M Piedvache A Børch K Huusom LD Bonamy AE Howell EA Effective Perinatal Intensive Care in Europe (EPICE) research group. Association of short antenatal corticosteroid administration-to-birth intervals with survival and morbidity among very preterm infants: results from the EPICE cohort JAMA Pediatr 2017 Jul 1 171 (7) 678 686 28505223 10.1001/jamapediatrics.2017.0602 PMC5710338 29 Crowther CA Middleton PF Voysey M Askie L Zhang S Martlow TK Effects of repeat prenatal corticosteroids given to women at risk of preterm birth: an individual participant data meta-analysis PLoS Med 2019 Apr 12 16 (4) e1002771 30978205 10.1371/journal.pmed.1002771 PMC6461224 30 Asztalos EV Murphy KE Willan AR Matthews SG Ohlsson A Saigal S Multiple courses of antenatal corticosteroids for preterm birth study: outcomes in children at 5 years of age (MACS-5) JAMA Pediatr 2013 Dec 167 (12) 1102 1110 24126948 10.1001/jamapediatrics.2013.2764 31 Räikkönen K Gissler M Kajantie E Associations between maternal antenatal corticosteroid treatment and mental and behavioral disorders in children JAMA 2020 May 19 323 (19) 1924 1933 32427304 10.1001/jama.2020.3937 PMC7237984 32 Paules C Pueyo V Martí E de Vilchez S Burd I Calvo P Threatened preterm labor is a risk factor for impaired cognitive development in early childhood Am J Obstet Gynecol 2017 Feb 216 (2) 157.e1 7 10.1016/j.ajog.2016.10.022 27780701 33 Jobe AH Kemp M Schmidt A Takahashi T Newnham J Milad M Antenatal corticosteroids: a reappraisal of the drug formulation and dose Pediatr Res 2021 89 (2) 318 325 33177675 10.1038/s41390-020-01249-w PMC7892336 34 Schmitz T Doret-Dion M Sentilhes L Parant O Claris O Renesme L Neonatal outcomes for women at risk of preterm delivery given half dose versus full dose of antenatal betamethasone: a randomised, multicentre, double-blind, placebo-controlled, non-inferiority trial Lancet 2022 20 400 (10352) 592 604 35988568 10.1016/S0140-6736(22)01535-5 35 Saugstad OD Delivery room management of term and preterm newly born infants Neonatology 2015 107 (4) 365 371 26044106 10.1159/000381159 36 Madar J Roehr CC Ainsworth S Ersdal H Morley C Rüdiger M European Resuscitation Council Guidelines 2021: newborn resuscitation and support of transition of infants at birth Resuscitation 2021 Apr 161 291 326 33773829 10.1016/j.resuscitation.2021.02.014 37 Murphy MC McCarthy LK O'Donnell CPF Crying and breathing by new-born preterm infants after early or delayed cord clamping Arch Dis Child Fetal Neonatal Ed 2020 May 105 (3) 331 333 31085675 10.1136/archdischild-2018-316592 38 Fogarty M Osborn DA Askie L Seidler AL Hunter K Lui K Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis Am J Obstet Gynecol 2018 Jan 218 (1) 1 18 29097178 10.1016/j.ajog.2017.10.231 39 Robledo KP Tarnow-Mordi WO Rieger I Suresh P Martin A Yeung C Effects of delayed versus immediate umbilical cord clamping in reducing death or major disability at 2 years corrected age among very preterm infants (APTS): a multicentre, randomised clinical trial Lancet Child Adolesc Health 2022 Mar 6 (3) 150 157 34895510 10.1016/S2352-4642(21)00373-4 40 Jasani B Torgalkar R Ye XY Syed S Shah PS Association of umbilical cord management strategies with outcomes of preterm infants: a systematic review and network meta-analysis JAMA Pediatr 2021 175 (4) e210102 33683307 10.1001/jamapediatrics.2021.0102 PMC7941254 41 Katheria A Reister F Essers J Mendler M Hummler H Subramaniam A Association of umbilical cord milking vs delayed umbilical cord clamping with death or severe intraventricular hemorrhage among preterm infants JAMA 2019 Nov 19 322 (19) 1877 1886 31742630 10.1001/jama.2019.16004 PMC6865839 42

Knol R Brouwer E van den Akker T DeKoninck P van Geloven N Polglase GR Physiological-based cord clamping in very preterm infants - randomised controlled trial on effectiveness of stabilisation Resuscitation 2020 Feb 1 147 26 33 31874212 10.1016/j.resuscitation.2019.12.007 43 Dekker J Hooper SB Martherus T Cramer SJE van Geloven N Te Pas AB Repetitive versus standard tactile stimulation of preterm infants at birth - a randomized controlled trial Resuscitation 2018 Jun 127 37 43 29580959 10.1016/j.resuscitation.2018.03.030 44 Dekker J Hooper SB van Vonderen JJ Witlox RSGM Lopriore E Te Pas AB Caffeine to improve breathing effort of preterm infants at birth: a randomized controlled trial Pediatr Res 2017 Aug 82 (2) 290 296 28288150 10.1038/pr.2017.45 45 Ines F Hutson S Coughlin K Hopper A Banerji A Uy C Multicentre, randomised trial of preterm infants receiving caffeine and less invasive surfactant administration compared with caffeine and early continuous positive airway pressure (CaLI trial): study protocol BMJ Open 2021 Jan 22 11 (1) e038343 10.1136/bmjopen-2020-038343 PMC7825253 33483435 46 Subramaniam P Ho JJ Davis PG Prophylactic or very early initiation of Continuous Positive Airway Pressure (CPAP) for preterm infants Cochrane Database Syst Rev 2021 Oct 18 10 (10) CD001243 34661278 10.1002/14651858.CD001243.pub4 PMC8521644 47 Bamat N Fierro J Mukerji A Wright CJ Millar D Kirpalani H Nasal continuous positive airway pressure levels for the prevention of morbidity and mortality in preterm infants Cochrane Database Syst Rev 2021 Nov 30 11 (11) CD012778 34847243 10.1002/14651858.CD012778.pub2 PMC8631577 48 Kirpalani H Ratcliffe SJ Keszler M Davis PG Foglia EE Te Pas A Effect of sustained inflations vs intermittent positive pressure ventilation on bronchopulmonary dysplasia or death among extremely preterm infants: the SAIL randomized clinical trial JAMA 2019 Mar 26 321 (12) 1165 1175 30912836 10.1001/jama.2019.1660 PMC6439695 49 Kuypers KLAM Lamberska T Martherus T Dekker J Böhlinger S Hooper SB The effect of a face mask for respiratory support on breathing in preterm infants at birth Resuscitation 2019 Nov 144 178 184 31521774 10.1016/j.resuscitation.2019.08.043 50 Mangat A Bruckner M Schmölzer GM Face mask versus nasal prong or nasopharyngeal tube for neonatal resuscitation in the delivery room: a systematic review and meta-analysis Arch Dis Child Fetal Neonatal Ed 2021 Sep 106 (5) 561 567 33504574 10.1136/archdischild-2020-319460 51 Donaldsson S Drevhammar T Li Y Bartocci M Rettedal SI Lundberg F Comparison of respiratory support after delivery in infants born before 28 Weeks' gestational age: the CORSAD randomized clinical trial JAMA Pediatr 2021 Sep 1 175 (9) 911 918 34125148 10.1001/jamapediatrics.2021.1497 PMC8424478 52 Abiramalatha T Ramaswamy VV Bandyopadhyay T Pullattayil AK Thanigainathan S Trevisanuto D Delivery room interventions for hypothermia in preterm neonates: a systematic review and network meta-analysis JAMA Pediatr 2021 Sep 1 175 (9) e210775 34028513 10.1001/jamapediatrics.2021.0775 PMC8145154 53 Cavallin F Doglioni N Allodi A Battajon N Vedovato S Capasso L Thermal management with and without servo-controlled system in preterm infants immediately after birth: a multicentre, randomised controlled study Arch Dis Child Fetal Neonatal Ed 2021 Nov 106 (6) 572 577 33597230 10.1136/archdischild-2020-320567 54 McCarthy LK Molloy EJ Twomey AR Murphy JF O'Donnell CP A randomized trial of exothermic mattresses for preterm newborns in polyethylene bags Pediatrics 2013 Jul 132 (1) e135 41 23776115 10.1542/peds.2013-0279 55 Thamrin V Saugstad OD Tarnow-Mordi W Wang YA Lui K Wright IM Preterm infant outcomes after randomization to initial resuscitation with FiO₂ 0.21 or 1.0 J Pediatr 2018 Oct 201 55 61 e1 30251639 10.1016/j.jpeds.2018.05.053 56 Kapadia V Oei JL Finer N Rich W Rabi Y Wright IM Outcomes of delivery room resuscitation of bradycardic preterm infants: a retrospective cohort study of randomised trials of high vs low initial oxygen concentration and an individual patient data analysis Resuscitation 2021 Oct 167 209 217 34425156 10.1016/j.resuscitation.2021.08.023 PMC8603874 57 Anton O Fernandez R Rendon-Morales E Aviles-Espinosa R Jordan H Rabe H Heart rate monitoring in newborn babies: a systematic review Neonatology 2019 116 (3) 199 210 31247620 10.1159/000499675 58 Abbey NV Mashruwala V Weydig HM Steven Brown L Ramon EL Ibrahim J Electrocardiogram for heart rate evaluation during preterm resuscitation at birth: a randomized trial Pediatr Res 2022 91 (6) 1445 1451 34645954 10.1038/s41390-021-01731-z PMC8513736 59 Hawkes GA Hawkes CP Kenosi M Demeulemeester J Livingstone V Ryan CA Auscultate, palpate and tap: time to re-evaluate Acta Paediatr 2016 Feb 105 (2) 178 182 26317177 10.1111/apa.13169 60 de Medeiros SM Mangat A Polglase GR Sarrato GZ Davis PG Schmölzer GM Respiratory function monitoring to improve the outcomes following neonatal resuscitation: a systematic review and meta-analysis Arch Dis Child Fetal Neonatal Ed 2022 Jan 20 107 (6) 589 596 35058279 10.1136/archdischild-2021-323017 61 Lui K Jones LJ Foster JP Davis PG Ching SK Oei JL Lower

versus higher oxygen concentrations titrated to target oxygen saturations during resuscitation of preterm infants at birth *Cochrane Database Syst Rev* 2018 May 4 5 (5) CD010239 29726010 10.1002/14651858.CD010239.pub2 PMC6494481 62 Saugstad OD Kapadia V Oei JL Oxygen in the first minutes of life in very preterm infants *Neonatology* 2021 118 (2) 218 224 33902059 10.1159/000516261 63 Dekker J Martherus T Lopriore E Giera M McGillick EV Hutten J The effect of initial high versus low FiO₂ on breathing effort in preterm infants at birth: a randomized controlled trial *Front Pediatr* 2019 Dec 12 7 504 31921719 10.3389/fped.2019.00504 PMC6927294 64 Herting E Härtel C Göpel W Less invasive surfactant administration: best practices and unanswered questions *Curr Opin Pediatr* 2020 Apr 32 (2) 228 234 32068592 10.1097/MOP.0000000000000878 PMC7077956 65 Evans P Shults J Weinberg DD Napolitano N Ades A Johnston L Intubation competence during neonatal fellowship training *Pediatrics* 2021 Jul 148 (1) e2020036145 34172556 10.1542/peds.2020-036145 PMC8290971 66 Garvey AA Dempsey EM Simulation in neonatal resuscitation *Front Pediatr* 2020 Feb 25 8 59 32158737 10.3389/fped.2020.00059 PMC7052260 67 O'Shea JE Kirolos S Thio M Kamlin COF Davis PG Neonatal videolaryngoscopy as a teaching aid: the trainees' perspective *Arch Dis Child Fetal Neonatal Ed* 2021 Mar 106 (2) 168 171 32963087 10.1136/archdischild-2020-319619 68 Walter-Nicolet E Courtois E Milesi C Ancel PY Beuchée A Tourneux P Premedication practices for delivery room intubations in premature infants in France: results from the EPIPAGE 2 cohort study *PLoS One* 2019 Apr 10 14 (4) e0215150 30970001 10.1371/journal.pone.0215150 PMC6457540 69 Norman M Jonsson B Wallström L Sindelar R Respiratory support of infants born at 22-24 weeks of gestational age *Semin Fetal Neonatal Med* 2022 Apr 27 (2) 101328 35400604 10.1016/j.siny.2022.101328 70 Stevens TP Harrington EW Blennow M Soll RF Early surfactant administration with brief ventilation versus selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome *Cochrane Database Syst Rev* 2007 Oct 2007 (4) CD003063 17943779 10.1002/14651858.CD003063.pub3 PMC8554819 71 Abdel-Latif ME Davis PG Wheeler KI De Paoli AG Dargaville PA Surfactant therapy via thin catheter in preterm infants with or at risk of respiratory distress syndrome *Cochrane Database Syst Rev* 2021 May 10 5 (5) CD011672 33970483 10.1002/14651858.CD011672.pub2 PMC8109227 72 De Luca D de Winter JP Less invasive surfactant administration: all that glitters is not gold *Eur J Pediatr* 2020 Aug 179 (8) 1295 1296 32462484 10.1007/s00431-020-03688-3 73 Dargaville PA Kamlin COF Orsini F Wang X De Paoli AG Kanmaz Kutman HG Effect of minimally invasive surfactant therapy vs sham treatment on death or bronchopulmonary dysplasia in preterm infants with respiratory distress syndrome: the OPTIMIST-A randomized clinical trial *JAMA* 2021 Dec 28 326 (24) 2478 2487 34902013 10.1001/jama.2021.21892 PMC8715350 74 Härtel C Herting E Humbert A Hanke K Mehler K Keller T Association of administration of surfactant using less invasive methods with outcomes in extremely preterm infants less than 27 Weeks of gestation *JAMA Netw Open* 2022 Aug 1 5 (8) e2225810 35943742 10.1001/jamanetworkopen.2022.25810 PMC9364126 75 Reynolds P Bustani P Darby C Fernandez Alvarez JR Fox G Jones S Less-invasive surfactant administration for neonatal respiratory distress syndrome: a consensus guideline *Neonatology* 2021 118 (5) 586 592 34515188 10.1159/000518396 76 Herting E Kribs A Härtel C von der Wense A Weller U Hoehn T Two-year outcome data suggest that Less Invasive Surfactant Administration (LISA) is safe. Results from the follow-up of the randomized controlled AMV (Avoid Mechanical Ventilation) study *Eur J Pediatr* 2020 Aug 179 (8) 1309 1313 32067100 10.1007/s00431-020-03572-0 PMC7351829 77 Federici C Fornaro G Roehr CC Cost-saving effect of early less invasive surfactant administration versus continuous positive airway pressure therapy alone for preterm infants with respiratory distress syndrome *Eur J Hosp Pharm* 2022 29 (6) 346 352 33658228 10.1136/ejhpharm-2020-002465 PMC9614139 78 Moschino L Ramaswamy VV Reiss IKM Baraldi E Roehr CC Simons SHP Sedation for less invasive surfactant administration in preterm infants: a systematic review and meta-analysis *Pediatr Res* 2022 Jun 2 10.1038/s41390-022-02121-9 35654833 79 Krajewski P Szepecht D Hojnowski R Premedication practices for less invasive surfactant administration - results from a nationwide cohort study *J Matern Fetal Neonatal Med* 2020 Dec 25 1 5 33356691 10.1080/14767058.2020.1863365 80 Roberts KD Brown R Lampland AL Leone TA Rudser KD Finer NN Laryngeal mask airway for surfactant administration in neonates: a randomized, controlled trial *J Pediatr* 2018 Feb 193 40 46 e1 29174079 10.1016/j.jpeds.2017.09.068 81 Gallup JA Ndakor SM Pezzano C Pinheiro JMB Randomized trial of surfactant therapy via laryngeal mask airway versus brief tracheal intubation in neonates born preterm *J Pediatr* 2022 Oct 12 3476 (22) S002200891 5

10.1016/j.jpeds.2022.10.009 36241051 82 Gaertner VD Thomann J Bassler D Rüegger CM Surfactant nebulization to prevent intubation in preterm infants: a systematic review and meta-analysis *Pediatrics* 2021 148 (5) e2021052504 34711678 10.1542/peds.2021-052504 83 Murphy MC Galligan M Molloy B Hussain R Doran P O'Donnell C Study protocol for the POPART study-prophylactic oropharyngeal surfactant for preterm infants: a randomised trial *BMJ Open* 2020 Jul 20 10 (7) e035994 10.1136/bmjopen-2019-035994 PMC7375508 32690739 84 Bahadue FL Soll R Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome *Cochrane Database Syst Rev* 2012 Nov 14 11 (11) CD001456 23152207 10.1002/14651858.CD001456.pub2 PMC7057030 85 Verder H Albertsen P Ebbesen F Greisen G Robertson B Bertelsen A Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation *Pediatrics* 1999 Feb 103 (2) E24 9925870 10.1542/peds.103.2.e24 86 Gulczyńska E Szczapa T Hojnowski R Borszewska-Kornacka MK Rutkowska M Fraction of inspired oxygen as a predictor of CPAP failure in preterm infants with respiratory distress syndrome: a prospective multicenter study *Neonatology* 2019 116 (2) 171 178 31112987 10.1159/000499674 PMC6878744 87 Dell'Orto V Nobile S Correani A Marchionni P Giretti I Rondina C Early nasal continuous positive airway pressure failure prediction in preterm infants less than 32 weeks gestational age suffering from respiratory distress syndrome *Pediatr Pulmonol* 2021 Dec 56 (12) 3879 3886 34610212 10.1002/ppul.25678 88 Wright CJ Glaser K Speer CP Härtel C Roehr CC Noninvasive ventilation and exogenous surfactant in times of ever decreasing gestational age: how do we make the most of these tools? *J Pediatr* 2022 247 138 146 35429507 10.1016/j.jpeds.2022.04.011 89 Capasso L Pacella D Migliaro F De Luca D Raimondi F Can lung ultrasound score accurately predict the need for surfactant replacement in preterm neonates? A systematic review and meta-analysis protocol *PLoS One* 2021 Jul 28 16 (7) e0255332 34320032 10.1371/journal.pone.0255332 PMC8318286 90 Heiring C Verder H Schousboe P Jessen TE Bender L Ebbesen F Predicting respiratory distress syndrome at birth using a fast test based on spectroscopy of gastric aspirates: 2. Clinical part *Acta Paediatr* 2020 Feb 109 (2) 285 290 31038796 10.1111/apa.14831 PMC7004016 91 Ramaswamy VV Abiramalatha T Bandyopadhyay T Boyle E Roehr CC Surfactant therapy in late preterm and term neonates with respiratory distress syndrome: a systematic review and meta-analysis *Arch Dis Child Fetal Neonatal Ed* 2022 Jul 107 (4) 393 397 34686533 10.1136/archdischild-2021-322890 92 Lanciotti L Correani A Pasqualini M Antognoli L Dell'Orto VG Giorgetti C Respiratory distress syndrome in preterm infants of less than 32 weeks: what difference does giving 100 or 200 mg/kg of exogenous surfactant make? *Pediatr Pulmonol* 2022 May 16 57 (9) 2067 2073 35577766 10.1002/ppul.25979 PMC9541469 93 Singh N Halliday HL Stevens TP Suresh G Soll R Rojas-Reyes MX Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants *Cochrane Database Syst Rev* 2015 Dec 2015 CD010249 26690260 10.1002/14651858.CD010249.pub2 PMC9465687 94 Ramanathan R Biniwale M Sekar K Hanna N Golombek S Bhatia J Synthetic surfactant CHF5633 compared with poractant alfa in the treatment of neonatal respiratory distress syndrome: a multicenter, double-blind, randomized, controlled clinical trial *J Pediatr* 2020 Oct 225 90 96 e1 32553868 10.1016/j.jpeds.2020.06.024 95 Zhong YY Li JC Liu YL Zhao XB Male M Song DK Early intratracheal administration of corticosteroid and pulmonary surfactant for preventing bronchopulmonary dysplasia in preterm infants with neonatal respiratory distress syndrome: a meta-analysis *Curr Med Sci* 2019 Jun 39 (3) 493 499 31209823 10.1007/s11596-019-2064-9 96 Askie LM Darlow BA Finer N Schmidt B Stenson B Tarnow-Mordi W Association between oxygen saturation targeting and death or disability in extremely preterm infants in the neonatal oxygenation prospective meta-analysis collaboration *JAMA* 2018 Jun 5 319 (21) 2190 2201 29872859 10.1001/jama.2018.5725 PMC6583054 97 Saugstad OD Oxygenation of the immature infant: a commentary and recommendations for oxygen saturation targets and alarm limits *Neonatology* 2018 114 (1) 69 75 29669357 10.1159/000486751 98 Liu T Tomlinson LA Yu Y Ying GS Quinn GE Binenbaum G Changes in institutional oxygen saturation targets are associated with an increased rate of severe retinopathy of prematurity *J AAPOS* 2022 Feb 26 (1) 18.e1 6 10.1016/j.jaapos.2021.10.002 35032651 99 Söderström F Normann E Holmström G Larsson E Ahlsson F Sindelar R Reduced rate of treated retinopathy of prematurity after implementing lower oxygen saturation targets *J Perinatol* 2019 Mar 39 (3) 409 414 30617284 10.1038/s41372-018-0300-y 100 Gentle SJ Abman SH Ambalavanan N Oxygen therapy and pulmonary hypertension in preterm infants *Clin Perinatol* 2019 46 (3) 611 619 31345551 10.1016/j.clp.2019.05.009 101 Ali SK Jayakar RV Marshall AP Gale TJ Dargaville PA Preliminary

study of automated oxygen titration at birth for preterm infants Arch Dis Child Fetal Neonatal Ed 2022 Feb 9 107 (5) 539 544 35140115 10.1136/archdischild-2021-323486 102 Claure N Bancalari E New modes of respiratory support for the premature infant: automated control of inspired oxygen concentration Clin Perinatol 2021 Dec 48 (4) 843 853 34774212 10.1016/j.clp.2021.08.002 103 Dargaville PA Marshall AP Ladlow OJ Bannink C Jayakar R Eastwood-Sutherland C Automated control of oxygen titration in preterm infants on non-invasive respiratory support Arch Dis Child Fetal Neonatal Ed 2022 Jan 107 (1) 39 44 33963005 10.1136/archdischild-2020-321538 104 Ramaswamy VV Abiramalatha T Bandyopadhyay T Shaik NB Pullattayil S AK Cavallin F Delivery room CPAP in improving outcomes of preterm neonates in low-and middle-income countries: a systematic review and network meta-analysis Resuscitation 2022 Jan 170 250 263 34757058 10.1016/j.resuscitation.2021.10.027 105 Ho JJ Subramaniam P Davis PG Continuous positive airway pressure (CPAP) for respiratory distress in preterm infants Cochrane Database Syst Rev 2020 Oct 15 10 (10) CD002271 33058208 10.1002/14651858.CD002271.pub3 PMC8094155 106 Subramaniam P Ho JJ Davis PG Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants Cochrane Database Syst Rev 2016 Jun 14 (6) CD001243 27315509 10.1002/14651858.CD001243.pub3 107 Owen LS Manley BJ Davis PG Doyle LW The evolution of modern respiratory care for preterm infants Lancet 2017 Apr 22 389 (10079) 1649 1659 28443559 10.1016/S0140-6736(17)30312-4 108 Backes CH Notestine JL Lamp JM Balough JC Notestine AM Alfred CM Evaluating the efficacy of Seattle-PAP for the respiratory support of premature neonates: study protocol for a randomized controlled trial Trials 2019 Jan 18 20 (1) 63 30658678 10.1186/s13063-018-3166-6 PMC6339409 109 Jensen CF Sellmer A Ebbesen F Cipliene R Johansen A Hansen RM Sudden vs pressure wean from nasal continuous positive airway pressure in infants born before 32 weeks of gestation: a randomized clinical trial JAMA Pediatr 2018 Sep 1 172 (9) 824 831 30039171 10.1001/jamapediatrics.2018.2074 PMC6143058 110 Falk M Gunnarsdottir K Baldursdottir S Donaldsson S Jonsson B Drevhammar T Interface leakage during neonatal CPAP treatment: a randomised, cross-over trial Arch Dis Child Fetal Neonatal Ed 2021 Nov 106 (6) 663 667 33963004 10.1136/archdischild-2021-321579 PMC8543197 111 Bashir T Murki S Kiran S Reddy VK Oleti TP Nasal mask' in comparison with "nasal prongs" or "rotation of nasal mask with nasal prongs" reduce the incidence of nasal injury in preterm neonates supported on nasal Continuous Positive Airway Pressure (nCPAP): a randomized controlled trial PLoS One 2019 Jan 31 14 (1) e0211476 30703172 10.1371/journal.pone.0211476 PMC6355017 112 Malakian A Aramesh MR Agahin M Dehdashtian M Non-invasive duo positive airway pressure ventilation versus nasal continuous positive airway pressure in preterm infants with respiratory distress syndrome: a randomized controlled trial BMC Pediatr 2021 Jul 6 21 (1) 301 34229655 10.1186/s12887-021-02741-w PMC8259388 113 Moretti C Gizzi C Synchronized nasal intermittent positive pressure ventilation Clin Perinatol 2021 Dec 48 (4) 745 759 34774207 10.1016/j.clp.2021.07.005 114 Ramaswamy VV More K Roehr CC Bandiya P Nangia S Efficacy of noninvasive respiratory support modes for primary respiratory support in preterm neonates with respiratory distress syndrome: systematic review and network meta-analysis Pediatr Pulmonol 2020 Nov 55 (11) 2940 2963 32762014 10.1002/ppul.25011 115 Ramaswamy VV Bandyopadhyay T Nanda D Bandiya P More K Oommen VI Efficacy of noninvasive respiratory support modes as postextubation respiratory support in preterm neonates: a systematic review and network meta-analysis Pediatr Pulmonol 2020 Nov 55 (11) 2924 2939 32757365 10.1002/ppul.25007 116 Fischer HS Bohlin K Bührer C Schmalisch G Cremer M Reiss I Nasal high-frequency oscillation ventilation in neonates: a survey in five European countries Eur J Pediatr 2015 Apr 174 (4) 465 471 25227281 10.1007/s00431-014-2419-y 117 Gaertner VD Waldmann AD Davis PG Bassler D Springer L Thomson J Lung volume distribution in preterm infants on non-invasive high-frequency ventilation Arch Dis Child Fetal Neonatal 2022 Jan 31 107 (5) 551 557 10.1136/archdischild-2021-322990 35101993 118 Li J Chen L Shi Y Nasal high-frequency oscillatory ventilation versus nasal continuous positive airway pressure as primary respiratory support strategies for respiratory distress syndrome in preterm infants: a systematic review and meta-analysis Eur J Pediatr 2022 Jan 181 (1) 215 223 34254173 10.1007/s00431-021-04190-0 119 Zhu XW Zhao JN Tang SF Yan J Shi Y Noninvasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in preterm infants with moderate-severe respiratory distress syndrome: a preliminary report Pediatr Pulmonol 2017 Aug 52 (8) 1038 1042 28672094 10.1002/ppul.23755 120 Roehr CC Yoder BA Davis PG Ives K Evidence support and guidelines for using heated, humidified, high-flow nasal cannulae in

Neonatology: oxford nasal high-flow therapy meeting Clin Perinatol 2015 2016 Dec 43 (4) 693 705 10.1016/j.clp.2016.07.006 27837753 121 Dysart K Miller TL Wolfson MR Shaffer TH Research in high flow therapy: mechanisms of action Respir Med 2009 Oct 103 (10) 1400 1405 19467849 10.1016/j.rmed.2009.04.007 122 Wilkinson D Andersen C O'Donnell CP De Paoli AG Manley BJ High flow nasal cannula for respiratory support in preterm infants Cochrane Database Syst Rev 2016 Feb 22 2 CD006405 26899543 10.1002/14651858.CD006405.pub3 PMC9371597 123 Roberts CT Owen LS Manley BJ Frøisland DH Donath SM Dalziel KM Nasal high-flow therapy for primary respiratory support in preterm infants N Engl J Med 2016 Sep 22 375 (12) 1142 1151 27653564 10.1056/NEJMoa1603694 124 Hodgson KA Manley BJ Davis PG Is nasal high flow inferior to continuous positive airway pressure for neonates? Clin Perinatol 2019 Sep 46 (3) 537 551 31345545 10.1016/j.clp.2019.05.005 125 Zivanovic S Scrivens A Panza R Reynolds P Laforgia N Ives KN Nasal high-flow therapy as primary respiratory support for preterm infants without the need for rescue with nasal continuous positive airway pressure Neonatology 2019 115 (2) 175 181 30513521 10.1159/000492930 126 Bruet S Butin M Dutheil F Systematic review of high-flow nasal cannula versus continuous positive airway pressure for primary support in preterm infants Arch Dis Child Fetal Neonatal Ed 2022 Jan 107 (1) 56 59 34016651 10.1136/archdischild-2020-321094 127 Firestone KS Beck J Stein H Neurally adjusted ventilatory assist for noninvasive support in neonates Clin Perinatol 2016 Dec 43 (4) 707 724 27837754 10.1016/j.clp.2016.07.007 128 Makker K Cortez J Jha K Shah S Nandula P Lowrie D Comparison of extubation success using Noninvasive Positive Pressure Ventilation (NIPPV) versus noninvasive neurally adjusted ventilatory assist (NI-NAVA) J Perinatol 2020 Aug 40 (8) 1202 1210 31911641 10.1038/s41372-019-0578-4 PMC7222927 129 Dargaville PA Gerber A Johansson S De Paoli AG Kamlin CO Orsini F Incidence and outcome of CPAP failure in preterm infants Pediatrics 2016 Jul 138 (1) e20153985 27365307 10.1542/peds.2015-3985 130 Chawla S Natarajan G Shankaran S Carper B Brion LP Keszler M Markers of successful extubation in extremely preterm infants, and morbidity after failed extubation J Pediatr 2017 Oct 189 113 119 e2 28600154 10.1016/j.jpeds.2017.04.050 PMC5657557 131 Klingenberg C Wheeler KI McCallion N Morley CJ Davis PG Volume-targeted versus pressure-limited ventilation in neonates Cochrane Database Syst Rev 2017 Oct 17 10 (10) CD003666 29039883 10.1002/14651858.CD003666.pub4 PMC6485452 132 Keszler M Nassabeh-Montazami S Abubakar K Evolution of tidal volume requirement during the first 3 weeks of life in infants <800 g ventilated with volume guarantee Arch Dis Child Fetal Neonatal Ed 2009 Jul 94 (4) F279 82 19060010 10.1136/adc.2008.147157 133 National Institute for Clinical Excellence Specialist neonatal respiratory care: evidence reviews for respiratory support FINAL (April 2019) <https://www.nice.org.uk/guidance/NG124> 35157413 134 Wallström L Sjöberg A Sindelar R Early volume targeted ventilation in preterm infants born at 22-25 weeks of gestational age Pediatr Pulmonol 2021 May 56 (5) 1000 1007 33611849 10.1002/ppul.25271 135 Hunt KA Dassios T Greenough A Proportional Assist Ventilation (PAV) versus neurally adjusted ventilator assist (NAVA): effect on oxygenation in infants with evolving or established bronchopulmonary dysplasia Eur J Pediatr 2020 Jun 179 (6) 901 908 31980954 10.1007/s00431-020-03584-w PMC7220976 136 Beck J Sinderby C Neurally adjusted ventilatory assist in newborns Clin Perinatol 2021 Dec 48 (4) 783 811 34774209 10.1016/j.clp.2021.07.007 137 Cools F Offringa M Askie LM Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants Cochrane Database Syst Rev 2015 Mar 19 (3) CD000104 25785789 10.1002/14651858.CD000104.pub4 PMC10711725 138 De Jaegere AP Deurloo EE van Rijn RR Offringa M van Kaam AH Individualized lung recruitment during high-frequency ventilation in preterm infants is not associated with lung hyperinflation and air leaks Eur J Pediatr 2016 Aug 175 (8) 1085 1090 27325148 10.1007/s00431-016-2744-4 PMC4930456 139 Iscan B Duman N Tuzun F Kumral A Ozkan H Impact of volume guarantee on high-frequency oscillatory ventilation in preterm infants: a randomized crossover clinical trial Neonatology 2015 108 (4) 277 282 26330156 10.1159/000437204 140 Garrido F Gonzalez-Caballero JL Lomax R Dady I The immediate efficacy of inhaled nitric oxide treatment in preterm infants with acute respiratory failure during neonatal transport Acta Paediatr 2020 Feb 109 (2) 309 313 31373038 10.1111/apa.14958 141 Aikio O Metsola J Vuolteenaho R Perhomaa M Hallman M Transient defect in nitric oxide generation after rupture of fetal membranes and responsiveness to inhaled nitric oxide in very preterm infants with hypoxic respiratory failure J Pediatr 2012 Sep 161 (3) 397 403 e1 22554621 10.1016/j.jpeds.2012.03.008 142 Blazek EV East CE Jauncey-Cooke J Bogossian F Grant CA Hough J Lung recruitment manoeuvres for reducing mortality and respiratory morbidity in

mechanically ventilated neonates Cochrane Database Syst Rev 2021 Mar 30 3 (3) CD009969 33781001 10.1002/14651858.CD009969.pub2 PMC8094588 143 Vento G Ventura ML Pastorino R van Kaam AH Carnielli V Cools F Lung recruitment before surfactant administration in extremely preterm neonates with respiratory distress syndrome (IN-REC-SUR-E): a randomised, unblinded, controlled trial Lancet Respir Med 2021 Feb 9 (2) 159 166 32687801 10.1016/S2213-2600(20)30179-X 144 Ferguson KN Roberts CT Manley BJ Davis PG Interventions to improve rates of successful extubation in preterm infants: a systematic review and meta-analysis JAMA Pediatr 2017 Feb 1 171 (2) 165 174 27918754 10.1001/jamapediatrics.2016.3015 145 Danan C Durrmeyer X Brochard L Decobert F Benani M Dassieu G A randomized trial of delayed extubation for the reduction of reintubation in extremely preterm infants Pediatr Pulmonol 2008 Feb 43 (2) 117 124 18092355 10.1002/ppul.20726 146 Shalish W Kanbar L Kovacs L Chawla S Keszler M Rao S Assessment of extubation readiness using spontaneous breathing trials in extremely preterm neonates JAMA Pediatr 2020 Feb 1 174 (2) 178 185 31860014 10.1001/jamapediatrics.2019.4868 PMC6990705 147 Gupta D Greenberg RG Sharma A Natarajan G Cotten M Thomas R A predictive model for extubation readiness in extremely preterm infants J Perinatol 2019 Dec 39 (12) 1663 1669 31455825 10.1038/s41372-019-0475-x 148 Buzzella B Claire N D'Ugard C Bancalari E A randomized controlled trial of two nasal continuous positive airway pressure levels after extubation in preterm infants J Pediatr 2014 Jan 164 (1) 46 51 24094879 10.1016/j.jpeds.2013.08.040 149 Schmidt B Roberts RS Davis P Doyle LW Barrington KJ Ohlsson A Long-term effects of caffeine therapy for apnea of prematurity N Engl J Med 2007 Nov 8 357 (19) 1893 1902 17989382 10.1056/NEJMoa073679 150 Davis PG Schmidt B Roberts RS Doyle LW Asztalos E Haslam R Caffeine for apnea of prematurity trial: benefits may vary in subgroups J Pediatr 2010 Mar 156 (3) 382 387 19926098 10.1016/j.jpeds.2009.09.069 151 Nylander Vujovic S Nava C Johansson M Bruschetti M Confounding biases in studies on early-versus late-caffeine in preterm infants: a systematic review Pediatr Res 2020 Sep 88 (3) 357 364 31931506 10.1038/s41390-020-0757-1 152 Elmowafi M Mohsen N Nour I Nasef N Prophylactic versus therapeutic caffeine for apnea of prematurity: a randomized controlled trial J Matern Fetal Neonatal Med 2021 Mar 26 1 9 10.1080/14767058.2021.1904873 33771081 153 Chavez L Bancalari E Caffeine: some of the evidence behind its use and abuse in the preterm infant Neonatology 2022 119 (4) 428 432 35691280 10.1159/000525267 154 Saroha V Patel RM Caffeine for preterm infants: fixed standard dose, adjustments for age or high dose? Semin Fetal Neonatal Med 2020 Dec 25 (6) 101178 33168464 10.1016/j.siny.2020.101178 PMC8096613 155 Woodgate PG Davies MW Permissive hypercapnia for the prevention of morbidity and mortality in mechanically ventilated newborn infants Cochrane Database Syst Rev 2001 2001 (2) CD002061 11406029 10.1002/14651858.CD002061 PMC7017931 156 Wong SK Chim M Allen J Butler A Tyrrell J Hurley T Carbon dioxide levels in neonates: what are safe parameters? Pediatr Res 2022 Apr 91 (5) 1049 1056 34230621 10.1038/s41390-021-01473-y PMC9122818 157 Doyle LW Cheong JL Hay S Manley BJ Halliday HL Late (≥ 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants Cochrane Database Syst Rev 2021 Oct 21 11 (11) CD001146 10.1002/14651858.CD001146.pub6 PMC8530019 34674229 158 Doyle LW Cheong JL Hay S Manley BJ Halliday HL Late (≥ 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants Cochrane Database Syst Rev 2021 Nov 11 11 (11) CD001145 34758507 10.1002/14651858.CD001145.pub5 PMC8580679 159 Doyle LW Halliday HL Ehrenkranz RA Davis PG Sinclair JC An update on the impact of postnatal systemic corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk of bronchopulmonary dysplasia J Pediatr 2014 Dec 165 (6) 1258 1260 25217197 10.1016/j.jpeds.2014.07.049 160 Doyle LW Davis PG Morley CJ McPhee A Carlin JB DART Study Investigators Low-dose dexamethasone facilitates extubation among chronically ventilator-dependent infants: a multicenter, international, randomized, controlled trial Pediatrics 2006 Jan 117 (1) 75 83 16396863 10.1542/peds.2004-2843 161 Doyle LW Davis PG Morley CJ McPhee A Carlin JB DART Study Investigators Outcome at 2 years of age of infants from the DART study: a multicenter, international, randomized, controlled trial of low-dose dexamethasone Pediatrics 2007 Apr 119 (4) 716 721 17403842 10.1542/peds.2006-2806 162 Shaffer ML Baud O Lacaze-Masmonteil T Peltoniemi OM Bonsante F Watterberg KL Effect of prophylaxis for early adrenal insufficiency using low-dose hydrocortisone in very preterm infants: an individual patient data meta-analysis J Pediatr 2019 Apr 207 136 142 e5 30416014 10.1016/j.jpeds.2018.10.004 163 Rousseau C Guichard M Saliba E Morel B Favrais G Duration of mechanical ventilation is more

critical for brain growth than postnatal hydrocortisone in extremely preterm infants Eur J Pediatr 2021 Nov 180 (11) 3307 3315 33993400 10.1007/s00431-021-04113-z 164 Renolleau C Toumazis A Bourmaud A Benoist JF Chevenne D Mohamed D Association between baseline cortisol serum concentrations and the effect of prophylactic hydrocortisone in extremely preterm infants J Pediatr 2021 Jul 234 65 70 e3 33359303 10.1016/j.jpeds.2020.12.057 165 Fontijn JR Bassler D Early systemic steroids in preventing bronchopulmonary dysplasia: are we moving closer to a benefit-risk-adapted treatment strategy? J Pediatr 2021 Jul 234 12 13 33592221 10.1016/j.jpeds.2021.02.024 166 Shah SS Ohlsson A Halliday HL Shah VS Inhaled versus systemic corticosteroids for preventing bronchopulmonary dysplasia in ventilated very low birth weight preterm neonates Cochrane Database Syst Rev 2017 Jan 4 10 (10) CD002058 29041034 10.1002/14651858.CD002058.pub3 PMC6485718 167 Ramaswamy VV Bandyopadhyay T Nanda D Bandiya P Ahmed J Garg A Assessment of postnatal corticosteroids for the prevention of bronchopulmonary dysplasia in preterm neonates: a systematic review and network meta-analysis JAMA Pediatr 2021 Jun 1 175 (6) e206826 33720274 10.1001/jamapediatrics.2020.6826 PMC7961472 168 Bassler D Shinwell ES Hallman M Jarreau PH Plavka R Carnielli V Long-term effects of inhaled budesonide for bronchopulmonary dysplasia N Engl J Med 2018 Jan 11 378 (2) 148 157 29320647 10.1056/NEJMoa1708831 169 Lemyre B Dunn M Thebaud B Postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia in preterm infants Paediatr Child Health 2020 Aug 25 (5) 322 331 32765169 10.1093/pch/pxaa073 PMC7395322 170 Bellù R Romantsik O Nava C de Waal KA Zanini R Bruschetti M Opioids for newborn infants receiving mechanical ventilation Cochrane Database Syst Rev 2021 Mar 17 3 (3) CD013732 33729556 10.1002/14651858.CD013732.pub2 PMC8121090 171 Ozawa Y Ades A Foglia EE DeMeo S Barry J Sawyer T Premedication with neuromuscular blockade and sedation during neonatal intubation is associated with fewer adverse events J Perinatol 2019 Jun 39 (6) 848 856 30940929 10.1038/s41372-019-0367-0 172 van Weteringen W van Essen T Gangaram-Panday NH Goos TG de Jonge RCJ Reiss IKM Validation of a new transcutaneous tcPO₂/tcPCO₂ sensor with an optical oxygen measurement in preterm neonates Neonatology 2020 117 (5) 628 636 32998134 10.1159/000510659 173 Greisen G Hansen ML Rasmussen MIS Vestager M Hyttel-Sørensen S Hahn GH Cerebral oximetry in preterm infants-to use or not to use, that is the question Front Pediatr 2022 Feb 2 9 747660 35186815 10.3389/fped.2021.747660 PMC8847778 174 de Siqueira Caldas JP Ferri WAG Marba STM Aragon DC Guinsburg R de Almeida MFB Admission hypothermia, neonatal morbidity, and mortality: evaluation of a multicenter cohort of very low birth weight preterm infants according to relative performance of the center Eur J Pediatr 2019 Jul 178 (7) 1023 1032 31056716 10.1007/s00431-019-03386-9 175 Sharma D Farahbakhsh N Sharma S Sharma P Sharma A Role of kangaroo mother care in growth and breast feeding rates in Very Low Birth Weight (VLBW) neonates: a systematic review J Matern Fetal Neonatal Med 2019 Jan 32 (1) 129 142 28274153 10.1080/14767058.2017.1304535 176 Prevention of Group B Streptococcal early-onset disease in newborns: ACOG committee opinion summary, number 797 Obstet Gynecol 2020 Feb 135 (2) 489 492 31977793 10.1097/AOG.0000000000003669 177 Rajar P Saugstad OD Berild D Dutta A Greisen G Lausten-Thomsen U Antibiotic stewardship in premature infants: a systematic review Neonatology 2020 117 (6) 673 686 33271554 10.1159/000511710 178 Capin I Hinds A Vomero B Roth P Blau J Are early-onset sepsis evaluations and empiric antibiotics mandatory for all neonates admitted with respiratory distress? Am J Perinatol 2022 Mar 39 (4) 444 448 32947642 10.1055/s-0040-1717070 179 Barrington KJ Management during the first 72 h of age of the periviable infant: an evidence-based review Semin Perinatol 2014 Feb 38 (1) 17 24 24468565 10.1053/j.semperi.2013.07.004 180 Hartnoll G Bétrémieux P Modi N Randomised controlled trial of postnatal sodium supplementation on body composition in 25 to 30 week gestational age infants Arch Dis Child Fetal Neonatal Ed 2000 Jan 82 (1) F24 8 10634837 10.1136/fn.82.1.F24 PMC1721041 181 Osborn DA Schindler T Jones LJ Sinn JK Bolisetty S Higher versus lower amino acid intake in parenteral nutrition for newborn infants Cochrane Database Syst Rev 2018 Mar 5 3 (3) CD005949 29505664 10.1002/14651858.CD005949.pub2 PMC6494253 182 Mihatsch WA Braegger C Bronsky J Cai W Campoy C Carnielli V ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition Clin Nutr 2018 Dec 37 (6 Pt B) 2303 2305 30471662 10.1016/j.clnu.2018.05.029 183 Kim K Kim NJ Kim SY Safety and efficacy of early high parenteral lipid supplementation in preterm infants: a systematic review and meta-analysis Nutrients 2021 May 2 13 (5) 1535 34063216 10.3390/nu13051535 PMC8147506 184 Morgan J Bombell S McGuire W Early trophic feeding versus enteral fasting for very preterm or

very low birth weight infants Cochrane Database Syst Rev 2013 Mar 28 (3) CD000504 23543508 10.1002/14651858.CD000504.pub4 PMC11480887 185 Oddie SJ Young L McGuire W Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants Cochrane Database Syst Rev 2021 8 (8) CD001241 34427330 10.1002/14651858.CD001241.pub8 PMC8407506 186 Quigley M Embleton ND McGuire W Formula versus donor breast milk for feeding preterm or low birth weight infants Cochrane Database Syst Rev 2019 Jul 19 7 (7) CD002971 31322731 10.1002/14651858.CD002971.pub5 PMC6640412 187 Dempsey E El-Khuffash A Clinical trials in hemodynamic support: past, present, and future Clin Perinatol 2020 Sep 47 (3) 641 652 32713455 10.1016/j.clp.2020.05.013 188 Thewissen L Naulaers G Hendriks D Caicedo A Barrington K Boylan G Cerebral oxygen saturation and autoregulation during hypotension in extremely preterm infants Pediatr Res 2021 Aug 90 (2) 373 380 33879849 10.1038/s41390-021-01483-w 189 Batton B Li L Newman NS Das A Watterberg KL Yoder BA Evolving blood pressure dynamics for extremely preterm infants J Perinatol 2014 Apr 34 (4) 301 305 24503912 10.1038/jp.2014.6 PMC3982788 190 Nestaas E Neonatologist performed echocardiography for evaluating the newborn infant Front Pediatr 2022 Mar 24 10 853205 35402362 10.3389/fped.2022.853205 PMC8987714 191 Finn D Roehr CC Ryan CA Dempsey EM Optimising intravenous volume resuscitation of the newborn in the delivery room: practical considerations and gaps in knowledge Neonatology 2017 112 (2) 163 171 28571020 10.1159/000475456 192 Subhedar NV Shaw NJ Dopamine versus dobutamine for hypotensive preterm infants Cochrane Database Syst Rev 2003 3 CD001242 10.1002/14651858.CD001242 12917901 193 Masumoto K Kusuda S Hemodynamic support of the micropreemie: should hydrocortisone never be left out? Semin Fetal Neonatal Med 2021 Jun 26 (3) 101222 33692008 10.1016/j.siny.2021.101222 194 Rozé JC Cambonie G Marchand-Martin L Gournay V Durrmeyer X Durox M Association between early screening for patent ductus arteriosus and in-hospital mortality among extremely preterm infants JAMA 2015 Jun 23-30 313 (24) 2441 2448 26103028 10.1001/jama.2015.6734 195 Liebowitz M Clyman RI Prophylactic indomethacin compared with delayed conservative management of the patent ductus arteriosus in extremely preterm infants: effects on neonatal outcomes J Pediatr 2017 Aug 187 119 126 e1 28396025 10.1016/j.jpeds.2017.03.021 PMC5533630 196 Ohlsson A Walia R Shah SS Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants Cochrane Database Syst Rev 2020 Feb 11 2 (2) CD003481 32045960 10.1002/14651858.CD003481.pub8 PMC7012639 197 Ohlsson A Shah PS Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants Cochrane Database Syst Rev 2020 Jan 27 1 (1) CD010061 31985831 10.1002/14651858.CD010061.pub4 PMC6984659 198 Mitra S Florez ID Tamayo ME Mbuagbaw L Vanniyasingam T Veroniki AA Association of placebo, indomethacin, ibuprofen, and acetaminophen with closure of hemodynamically significant patent ductus arteriosus in preterm infants: a systematic review and meta-analysis JAMA 2018 Mar 27 319 (12) 1221 1238 29584842 10.1001/jama.2018.1896 PMC5885871 199 Juujärvi S Saarela T Pokka T Hallman M Aikio O Intravenous paracetamol for neonates: long-term diseases not escalated during 5 years of follow-up Arch Dis Child Fetal Neonatal Ed 2021 Mar 106 (2) 178 183 32943529 10.1136/archdischild-2020-319069 200 Schmidt B Davis P Moddemann D Ohlsson A Roberts RS Saigal S Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants N Engl J Med 2001 Jun 28 344 (26) 1966 1972 11430325 10.1056/NEJM200106283442602 201 Hundscheid T Donders R Onland W Kooi EMW Vijlbrief DC de Vries WB Multi-centre, randomised non-inferiority trial of early treatment versus expectant management of patent ductus arteriosus in preterm infants (the BeNeDuctus trial): statistical analysis plan Trials 2021 Sep 15 22 (1) 627 34526095 10.1186/s13063-021-05594-x PMC8444433 202 Weisz DE Mirea L Rosenberg E Jang M Ly L Church PT Association of patent ductus arteriosus ligation with death or neurodevelopmental impairment among extremely preterm infants JAMA Pediatr 2017 May 1 171 (5) 443 449 28264088 10.1001/jamapediatrics.2016.5143 PMC5470355 203 Kirpalani H Bell EF Hintz SR Tan S Schmidt B Chaudhary AS Higher or lower hemoglobin transfusion thresholds for preterm infants N Engl J Med 2020 Dec 31 383 (27) 2639 2651 33382931 10.1056/NEJMoa2020248 PMC8487591 204 Franz AR Engel C Bassler D Rüdiger M Thome UH Maier RF Effects of liberal vs restrictive transfusion thresholds on survival and neurocognitive outcomes in extremely low-birth-weight infants: the ETTNO randomized clinical trial JAMA 2020 Aug 11 324 (6) 560 570 32780138 10.1001/jama.2020.10690 PMC7420159 205 Bell EF Red cell transfusion thresholds for preterm infants: finally some answers Arch Dis Child Fetal Neonatal Ed

2022 Mar 107 (2) 126 130 33906941 10.1136/archdischild-2020-320495 206 Deshpande S
 Suryawanshi P Ahya K Maheshwari R Gupta S Surfactant therapy for early onset pneumonia in late
 preterm and term neonates needing mechanical ventilation J Clin Diagn Res 2017 Aug 11 (8) SC09
 12 28969229 10.7860/JCDR/2017/28523.10520 PMC5620870 207 Aziz A Ohlsson A Surfactant for
 pulmonary haemorrhage in neonates Cochrane Database Syst Rev 2020 Feb 3 2 (2) CD005254
 32012227 10.1002/14651858.CD005254.pub4 PMC6996938 208 El Shahed Al Dargaville PA
 Ohlsson A Soll R Surfactant for meconium aspiration syndrome in term and late preterm infants
 Cochrane Database Syst Rev 2014 Dec 14 2014 (12) CD002054 25504256
 10.1002/14651858.CD002054.pub3 PMC7027383 209 Hascoët JM Picaud JC Ligi I Blanc T
 Moreau F Pinturier MF Late surfactant administration in very preterm neonates with prolonged
 respiratory distress and pulmonary outcome at 1 Year of age: a randomized clinical trial JAMA
 Pediatr 2016 Apr 170 (4) 365 372 26928567 10.1001/jamapediatrics.2015.4617 210 Williams E
 Greenough A Respiratory support of infants with congenital diaphragmatic hernia Front Pediatr
 2021 Dec 24 9 808317 35004552 10.3389/fped.2021.808317 PMC8740288 Table 1
 Representations of quality of evidence and strength of recommendations