B. Care for complications

B.1 CONTINUOUS POSITIVE AIRWAY PRESSURE FOR RESPIRATORY DISTRESS SYNDROME

Recommendation and remarks

RECOMMENDATION B.1 (UPDATED)

Continuous positive airway pressure (CPAP) therapy is recommended in preterm infants with clinical signs of respiratory distress syndrome. *(Strong recommendation, moderate-certainty evidence)*

Remarks

- The GDG noted that the evidence on harms (increased pneumothorax) was of uncertain clinical significance and the overall certainty of the body of evidence was low due to imprecision and indirectness.
- The GDG noted that there were limited data on the timing of initiation and duration of CPAP. Based on most of the trials included in the evidence review, the GDG suggests that CPAP may be considered as soon as the diagnosis of respiratory distress syndrome (RDS) is clinically suspected, and that duration should be based on clinical judgement.
- The GDG also noted that CPAP implementation must be done with skilled staff, quality equipment and quality consumables (including humidified blended oxygen–air and monitors).
- The GDG decided not to make a separate recommendation on the timing of CPAP for infants with RDS.

Background and definitions

Respiratory distress syndrome (RDS) is a major cause of morbidity and mortality in preterm infants *(146)*. RDS commonly develops in the first hours after birth and develops or "becomes established" over the first few days after birth *(146-148)*. Until the 1970s, initial therapy for RDS was traditionally oxygen given through a head box or nasal prongs, and infants with severe disease received mechanical ventilation.

Continuous positive airway pressure (CPAP) involves connecting a nasal "interface" (prongs, face mask or head box) via tubing to a pressure source with an air–oxygen mix *(149,150)*. CPAP provides distending pressure into the upper and lower airways preventing collapse, especially during expiration. CPAP devices were adapted for use in preterm babies in the 1970s and CPAP is now routinely used for preterm babies with RDS in many health-care facilities globally.

Summary of the evidence

OVERVIEW	B.1a Any CPAP	B.1b Early CPAP
PICO	**Population** – Preterm infants with RDS **Intervention 1** – Any CPAP **Comparator 1** – Usual supplemental oxygen therapy by head box, face mask or nasal cannula **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up	**Population** – Preterm infants with RDS **Intervention 2** – Early CPAP **Comparator 2** – Delayed CPAP **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – From birth **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)	

Effectiveness: Comparison 1 – Any CPAP versus supplemental oxygen

Sources and characteristics of the evidence

The effectiveness evidence for this comparison was derived from a Cochrane systematic review of five RCTs conducted in the 1970s and 1980s reporting on a total of 322 preterm infants *(151)*. An updated search conducted on 1 October 2021 located no new trials.

Four studies were conducted in high-income settings (Australia, the United Kingdom and the USA) and one in a low-resource setting (the United Republic of Tanzania). Infants were included if they had RDS (defined as an infant needing FiO_2 [fraction of inspired oxygen] > 0.30). All trials used traditional CPAP as the intervention, none used "bubble" or newer types of CPAP. The comparator in all the trials was supplemental oxygen. No infants received mechanical ventilation in the control group. The mean age at study entry ranged from 10 to 150 hours post-birth. The mean birth weight of infants was 1.7–2.0 kg, with two trials excluding infants weighing less than 1.0 kg at birth.

Critical outcomes

For any CPAP compared with supplemental oxygen for RDS, five trials reported all-cause mortality outcomes, five trials reported morbidity (3 reported use of mechanical ventilation, 5 "failed treatment", 4 pneumothorax, 2 bronchopulmonary dysplasia). No trials reported growth or neurodevelopment outcomes. (Full details are provided in GRADE Table B.1a, in the Web Supplement.)

- **Mortality:** Moderate-certainty evidence from five trials totalling 322 participants suggests a decrease in all-cause mortality by hospital discharge (RR 0.53, 95% CI 0.34 to 0.83).
- **Morbidity:** Very-low-certainty evidence from three trials totalling 233 participants suggests a decrease in the use of mechanical ventilation by hospital discharge (RR 0.72, 95% CI 0.54 to 0.96). Very-low-certainty evidence from five trials totalling 322 participants suggests a decrease in "failed treatment" (a composite outcome of death or the use of mechanical ventilation) by hospital discharge (RR 0.64, 95% CI 0.50 to 0.82). Low-certainty evidence from four trials totalling 270 participants suggests an increase in pneumothorax by hospital discharge (RR 2.48, 95% CI 1.16 to 5.30). Very-low-certainty evidence from two trials totalling 209 participants suggests little or no effect on bronchopulmonary dysplasia (defined as oxygen dependency at 28 days) by 36 weeks PMA (RR 1.04, 95% CI 0.35 to 3.13).

Other outcomes

One trial reported a decrease in the composite outcome of death or abnormal blood gases by hospital discharge (RR 0.53, 95% CI 0.32 to 0.90; 1 trial, 24 infants). One trial reported a decrease in the outcome of "transfer to an NICU" by hospital discharge (RR 0.49, 95% CI 0.30 to 0.78; 1 trial, 24 infants). One trial reported a decrease in the duration of oxygen therapy by hospital discharge (MD 0.20 days, 95% CI –2.47 to 2.87; 1 trial, 24 infants).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Effectiveness: Comparison 2 – Early versus delayed CPAP

Sources and characteristics of the evidence

The effectiveness evidence for this comparison was derived from a systematic review of four trials (2 RCTs and 2 quasi-RCTs) that recruited 119 preterm infants with RDS (mean birth weight 1.5–2.1 kg, mean gestational age 31–34 weeks) conducted in the United Kingdom and the USA in the 1970s or the early 1980s *(152)*. An updated search conducted on 1 October 2021 located no new trials. Infants were eligible for inclusion if they were given a diagnosis of RDS (based on clinical and radiological criteria) and were breathing spontaneously. Infants were randomized to receive CPAP immediately as soon as the diagnosis of RDS was made ("early group") or for treatment to be delayed until deterioration as defined by the study ("delayed group"). The early CPAP group received CPAP at a mean age of 7–18 hours post-birth and required FiO_2 0.30 to 0.60. The delayed CPAP group required FiO_2 from 0.60 to 1.0 but the mean age of receipt of CPAP was not stated in any trial.

Critical outcomes

For early compared with delayed CPAP for RDS, four trials reported all-cause mortality, four trials reported morbidity (4 reported the use of mechanical ventilation, 3 pneumothorax, 1 bronchopulmonary dysplasia). No trials reported growth or neurodevelopment outcomes. (Full details are provided in GRADE Table B.1b, in the Web Supplement.)

- **Mortality:** Low-certainty evidence from four trials totalling 119 participants suggests little or no effect on all-cause mortality by hospital discharge (RR 0.93, 95% CI 0.43 to 2.03).
- **Morbidity:** Very-low-certainty evidence from four trials totalling 119 participants suggests a decrease in the use of mechanical ventilation by hospital discharge ((RR 0.77, 95% CI 0.43 to 1.38). Low-certainty evidence from two trials totalling 98 participants suggests little or no effect on pneumothorax (RR 1.09, 95% CI 0.39 to 3.04). Very-low-certainty evidence from one trial with 29 participants suggests an increase in bronchopulmonary dysplasia at 36 weeks PMA (RR 1.42, 95% CI 0.10 to 20.49).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Other studies

Two studies assessing the effect of continuous negative pressure *(153,154)* were included in the previous Cochrane review *(155)* but not in the updated Cochrane review *(152)*, due to a change in the PICO intervention from negative pressure to continuous positive airway pressure (CPAP). The Cochrane review also excluded two RCTs *(156,157)* because they provided very early CPAP at 5 minutes of age, which was considered to be earlier that RDS could be established in the babies. These two RCTs were included in the 2021 Cochrane review of prophylactic and very early CPAP by Subramaniam et al. (see Recommendation B.1) *(158)*.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that carers want assistance in interacting with their babies, especially when they are undergoing therapies that make it difficult to have physical contact *(14)*. They want to learn about the health-care setting where they need to stay and care for their baby. They want to understand what medical equipment is being used and why. Studies report that families can find mechanical ventilation and CPAP intimidating and frightening and that these therapies can accentuate their feelings of inadequacy and lack of control over their baby's health care *(147,159)*. Families also worry about the pain and discomfort their baby is experiencing in NICUs *(14)*. No other specific evidence was located about whether families value CPAP rather than supplemental oxygen for their preterm or LBW baby or whether they find CPAP more or less acceptable than other supplemental oxygen.

Resources required and implementation considerations

Organization of care

CPAP for preterm or LBW infants should be done in special or intensive care units (level 2 or 3 facilities).

Infrastructure, equipment and supplies

CPAP devices include a pressure source with an air–oxygen mix . CPAP devices include "bubble" (underwater, water-seal) CPAP, ventilator CPAP and "Infant Flow Driver" CPAP. CPAP also requires an "interface", which is commonly a mask or nasal prongs. Disposable tubes and suction catheters are also needed. National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers who are qualified to work in level 2 (special newborn care units, special care nurseries) and level 3 (intensive care) facilities can support the provision of CPAP. Standardized packages are needed for training, supervision and monitoring.

Feasibility and equity

There was no specific evidence on the feasibility and equity of providing CPAP for preterm or LBW infants.

Summary of judgements

	Comparison 1. Any CPAP vs supplemental oxygen (B1.a)	Comparison 2. Early vs delayed CPAP (B1.b)
Justification	• Evidence of moderate benefits: decreased mortality *(moderate-certainty evidence)*, decreased mechanical ventilation *(very-low-certainty evidence)* and decreased "failed treatment", i.e. death or use of mechanical ventilation *(very-low-certainty evidence)* • Evidence of small harms: increased pneumothorax *(low-certainty evidence)* • Evidence of little or no effect on bronchopulmonary dysplasia *(very-low-certainty evidence)*	• Evidence of small benefits: decrease in use of mechanical ventilation *(very-low-certainty)* • Evidence of small harm: increase in bronchopulmonary dysplasia *(very-low-certainty evidence)* • Evidence of little or no effect on mortality and air leak (pneumothorax) *(low-certainty evidence)* • No evidence on other critical outcomes
Evidence-to-Decision summary		
Benefits	Moderate	Unknown
Harms	Small	Unknown
Certainty	Low	Very low
Balance	Favours CPAP	Unknown
Values	No uncertainty or variability about outcomes	Unknown
Acceptability	Probably yes	Unknown
Resources	Large	Negligible
Feasibility	Varies	Probably feasible
Equity	Varies	Probably equitable