B.4 METHYLXANTHINES FOR TREATMENT OF APNOEA

Recommendation and remarks

RECOMMENDATION B.4 (NEW)

Caffeine is recommended for the treatment of apnoea in preterm infants. *(Strong recommendation, moderate-certainty evidence)*

Remarks

- The GDG noted that evidence was available for all preterm infants, so caffeine (or other methylxanthines) is recommended for treatment of apnoea in preterm infants.
- The GDG noted that there were limited data on the dose, timing of initiation and duration of administration. Based on the largest trial *(169)* included in the evidence review, the GDG suggested a 20 mg/kg loading dose and a 5 mg/kg per day maintenance dose for six weeks. The duration of caffeine administration should be based on clinical judgement.
- If caffeine is not available, other methylxanthines (aminophylline or theophylline) may be considered.

Background and definitions

Apnoea (temporary cessation of breathing) is common in preterm infants *(170,171)*. The frequency of apnoea is inversely related to gestational age, and it occurs in almost all infants born before 28 weeks' gestation (extremely preterm) *(170,171)*. Episodes of apnoea can result in hypoxaemia and bradycardia requiring mechanical ventilation. Intermittent hypoxic episodes in the first two months after birth are associated with increased risk of chronic conditions, such as retinopathy of prematurity, and adverse neurodevelopmental outcomes *(172,173)*. Since the 1970s, methylxanthine medicines such as theophylline, aminophylline and caffeine have been used to manage apnoea. More recently, large pragmatic studies have included methylxanthine treatment for a variety of indications, including the treatment and prevention of apnoea *(174)*. Studies have also assessed the use of methylxanthines to prevent apnoea before and after extubation *(169,175)*.

Summary of the evidence

OVERVIEW	B.4 Methylxanthines for treatment of apnoea
PICO	**Population** – Preterm infants **Intervention** – Any methylxanthine (aminophylline, theophylline, caffeine) at any dose **Comparator** – Placebo or no methylxanthine treatment **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **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 – Methylxanthine for treatment of apnoea versus placebo or no methylxanthine treatment

Sources and characteristics of the evidence

The effectiveness evidence for this comparison was derived from a Cochrane review of 18 RCTs enrolling a total of 2705 preterm infants who received methylxanthines for any indication *(174)*. For the indication relevant to this comparison (for treatment of apnoea), the inclusion criteria for infants were gestational age at birth below 37 weeks and evidence of apnoea. Six RCTs were included, enrolling a total of 959 preterm infants from six countries (Australia, Canada, France, India, the United Kingdom and the USA). The largest study, the Caffeine for Apnoea of Prematurity (CAP) trial *(169)*, enrolled 767 participants (birth weight 0.5–1.2 kg) from nine countries who received methylxanthines for

treatment of apnoea and conducted follow-up after five years. The other five trials were small, with fewer than 100 infants in each trial.

Critical outcomes

For methylxanthines for treatment of apnoea compared with placebo or no methylxanthine treatment, three trials reported all-cause mortality, five reported morbidity (1 reported apnoea, 5 use of mechanical ventilation, 1 bronchopulmonary dysplasia) and one trial reported a composite outcome of death or major neurodevelopmental disability. No trials reported growth outcomes. (Full details are provided in GRADE Table B.4, in the Web Supplement.)

- **Mortality:** Low-certainty evidence from three trials totalling 154 participants suggests a decrease in all-cause mortality by hospital discharge (RR 0.49, 95% CI 0.14 to 1.78).
- **Morbidity:** Very-low-certainty evidence from one trial with 43 participants suggests a decrease in any apnoeic episodes by hospital discharge (RR 0.70, 95% CI 0.30 to 1.62). Low-certainty evidence from five trials totalling 192 participants suggests a decrease in the use of mechanical ventilation by hospital discharge (RR 0.34, 95% CI 0.12 to 0.97). Moderate-certainty evidence from one trial with 805 participants suggests a decrease in bronchopulmonary dysplasia at 36 weeks PMA (RR 0.72, 95% CI 0.58 to 0.89).
- **Mortality or neurodevelopment:** Moderate-certainty evidence from one trial with 767 participants suggests little or no effect on the composite outcome of death or major neurodevelopmental disability by the latest follow-up (5 years) (RR 0.85, 95% CI 0.71 to 1.01). This composite outcome was defined as death or survival to 5 years with one or more of the following: motor impairment (defined as a gross motor function classification system level of 3–5), cognitive impairment (defined as a full-scale IQ < 70), behaviour problems, poor general health, deafness and/or blindness, all measured using validated tests.

Subgroup analyses

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

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 (within a theme on the health-care environment) that carers want mechanisms and initiatives to help them to interact with their babies, especially when they are undergoing therapies that make it difficult to have physical contact with the infant *(14)*. They also want to learn about the health-care setting (including the equipment in use) where they need to stay and care for the infant. No other specific evidence was located about whether families value methylxanthines for their preterm or LBW baby or whether they find them more or less acceptable than other medicines or no treatment.

Resources required and implementation considerations

Organization of care

Methylxanthines (caffeine, theophylline and aminophylline) must be dispensed by a health worker. They can be provided in the health-care facility or at home. Caffeine is given once a day and theophylline and aminophylline are given three times a day.

Infrastructure, equipment and supplies

Methylxanthines are available as intravenous and oral formulations. Caffeine citrate is available as 20 mg/ml and 10 mg/ml for intravenous and oral use, respectively. Oral caffeine comes as a ready-to-use formulation that needs no mixing. Theophylline is available as 50–60 mg/5 ml liquid. Aminophylline is available as 25 mg/ml ampoules.

Workforce, training, supervision and monitoring

Health workers at all levels can support mothers and families. Standardized packages are needed for training, supervision and monitoring. Dispensing needs to be documented in clinical records.

Feasibility and equity

Studies report that availability and cost are barriers for the use of caffeine citrate formulations in LMICs *(176)*. Theophylline and aminophylline are more widely available than caffeine in LMICs *(31,176)*. There was no specific evidence on the feasibility and equity of providing methylxanthines for preterm or LBW infants.

Summary of judgements

Comparison: Methylxanthine for the treatment of apnoea in preterm infants vs placebo or no methylxanthine treatment (B.4)	
Justification	• Evidence of moderate benefits: decreased death, bronchopulmonary dysplasia *(moderate-certainty evidence)*, decreased mechanical ventilation *(low-certainty evidence)* and decreased neurodevelopmental disability *(moderate-certainty evidence)* • No evidence of harms

Evidence-to-Decision summary	
Benefits	Moderate
Harms	Trivial or none
Certainty	Moderate
Balance	Favours methylxanthines for treatment of apnoea in infants < 37 weeks
Values	No uncertainty or variability about outcomes
Acceptability	Acceptable
Resources	Low to moderate
Feasibility	Probably feasible
Equity	Probably equitable