B.6 METHYLXANTHINES FOR PREVENTION OF APNOEA

Recommendation and remarks

RECOMMENDATION B.6 (NEW)

Caffeine may be considered for the prevention of apnoea in preterm infants born before 34 weeks' gestation. *(Conditional recommendation, low-certainty evidence)*

Remarks

- The GDG noted that the evidence on increased mortality came from three small trials totalling 129 infants *(177-179)* and was uncertain due to very low quality, and imprecision. Also, data on "death alone" were not available from a large trial of 423 infants *(169)*, which reported no effect on a combined outcome of death and neurodevelopmental disability. The GDG also noted that the evidence on harms from increased use of mechanical ventilation was uncertain due to very low quality, and imprecision.
- The recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- The GDG noted that evidence was available only for preterm infants born before 34 weeks' gestation, but suggests that caffeine (or other methylxanthines) may also be considered for prevention of apnoea in preterm infants born at or after 34 weeks and before 37 weeks if there is clinical indication.
- 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

Please refer to the information in section B.4.

Summary of the evidence

OVERVIEW	B.6 Methylxanthines for prevention of apnoea
PICO	**Population** – Preterm infants (< 34 weeks) **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 – Methylxanthines for prevention of apnoea versus placebo or no methylxanthine treatment

Sources and characteristics of the evidence

The effectiveness evidence for this comparison was derived the same Cochrane review of preterm infants who received methylxanthines for any indication *(174)*. For the indication relevant to this comparison (for prevention of apnoea), the inclusion criteria for infants were gestational age at birth below 34 weeks and no evidence of apnoea. Seven RCTs enrolling a total of 706 preterm infants were included from six countries (Australia, Canada, the Islamic Republic of Iran, Switzerland, the United Kingdom and the USA). The largest study was also the CAP trial, which followed up 423 participants who received methylxanthines for prevention of apnoea *(169)*. The other six trials were small, with fewer than 100 infants in each.

Critical outcomes

For methylxanthines for prevention of apnoea compared with no methylxanthines, three trials reported all-cause mortality, four reported morbidity (2 reported apnoea, 4 use of mechanical ventilation, 3 bronchopulmonary dysplasia) and one reported a composite outcome of death or neurodevelopmental disability. No trials reported growth outcomes. (Full details are provided in GRADE Table B.6, in the Web Supplement.)

- **Mortality:** Low-certainty evidence from three trials *(177-179)* totalling 129 participants suggests little or no effect on mortality by hospital discharge (RR 2.19, 95% CI 0.85 to 5.68).
- **Morbidity:** Low-certainty evidence from two trials totalling 104 participants suggests a decrease in any apnoeic episodes by hospital discharge (RR 0.19, 95% CI 0.09 to 0.41). Low-certainty evidence from four trials totalling 208 participants suggests little or no effect on the use of mechanical ventilation by hospital discharge (RR 1.33, 95% CI 0.48 to 3.72). Moderate-certainty evidence from three trials totalling 541 participants suggests a decrease in bronchopulmonary dysplasia (defined as the use of supplemental oxygen at 36 weeks PMA) (RR 0.78, 95% CI 0.63 to 0.97).
- **Mortality or neurodevelopment:** Moderate-certainty evidence from one trial with 423 participants suggests no effect on the composite outcome of death or neurodevelopmental disability (see section B.4 for the definition of the composite outcome) by latest follow-up (5 years) (RR 1.00, 95% CI 0.80 to 1.24). Data on death alone and neurodevelopmental disability alone were not available for this trial.

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, resources, feasibility and equity

Please refer to the information on these topics in section B.4.

Summary of judgements

Comparison: Methylxanthine for the prevention of apnoea in preterm infants vs placebo or no methylxanthine treatment (B.6)	
Justification	In trials where most participants are infants born < 34 weeks' gestation: • Evidence of small-to-moderate benefit: decreased bronchopulmonary dysplasia *(moderate-certainty evidence)* and decreased apnoeic episodes *(low-certainty evidence)* • Evidence of harms uncertain: little or no effect on mortality *(low-certainty evidence)*, little or no effect on combined outcome of neurodevelopment or death *(moderate-certainty evidence)* and increase in use of mechanical ventilation *(low-certainty evidence)* • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Small to moderate
Harms	Unknown
Certainty	Low
Balance	Probably favours methylxanthines for prevention of apnoea in infants < 34 weeks
Values	Uncertainty or variability about outcomes
Acceptability	Varies
Resources	Low to moderate
Feasibility	Probably feasible
Equity	Probably equitable