B.5 METHYLXANTHINES FOR EXTUBATION

Recommendation and remarks

RECOMMENDATION B.5 (NEW)

Caffeine is recommended for the extubation of preterm infants born before 34 weeks' gestation. *(Strong recommendation, moderate-certainty evidence)*

Remarks

- 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 extubation of preterm infants born at or after 34 weeks and before 37 weeks, depending on clinical judgement.
- The GDG noted that there were limited data on the timing of initiation and duration of administration. Based on the largest trials *(169,175)* included in the evidence review, the GDG suggested starting caffeine 24 hours before a planned extubation. If the extubation is unplanned, the infant should receive the caffeine as soon as possible after the extubation and within 6 hours, and should continue to receive it for six days.
- The GDG noted that there were limited data on the dosage. Based on the largest trials *(169,175)* included in the evidence review, the GDG suggested a 20 mg/kg loading dose and 5 mg/kg per day maintenance dose for six days.
- 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.5 Methylxanthines for extubation
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 – Methylxanthine for extubation versus placebo or no methylxanthine treatment

Sources and characteristics of the evidence

The effectiveness evidence for this comparison was derived from the same Cochrane review of preterm infants who received methylxanthines for any indication *(174)*. For the indication relevant to this comparison (for extubation), the inclusion criteria for infants were gestational age at birth below 34 weeks and planned extubation. Seven RCTs enrolling a total of 870 preterm infants were included from five countries (Australia, Canada, Spain, the United Kingdom and the USA). The largest study was also the CAP trial *(169)*, which followed up 676 participants who received methylxanthines for extubation. The other six trials were small, with fewer than 100 infants in each trial.

Critical outcomes

For methylxanthines for extubation compared with no methylxanthine treatment, six trials reported morbidity (6 reported "failed extubation", 2 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.5, in the Web Supplement.)

- **Morbidity:** Moderate-certainty evidence from six trials totalling 197 participants suggests decreased failed extubation (defined as the infant having to be re-intubated) by hospital discharge (RR 0.48, 95% CI 0.32 to 0.71). Moderate-certainty evidence from two trials totalling 704 participants suggests a decrease in bronchopulmonary dysplasia (defined as a need for supplemental oxygen) by 36 weeks PMA (RR 0.81, 95% CI 0.70 to 0.92).
- **Mortality or neurodevelopment:** Moderate-certainty evidence from one trial with 676 participants suggests decreased death or major neurodevelopmental disability (see section B.4 for the definition of the composite outcome) by the latest follow-up (5 years) (RR 0.85, 95% CI 0.73 to 0.99).

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 extubation in preterm infants vs placebo or no methylxanthine treatment (B.5)	
Justification	In trials where most participants are infants born < 34 weeks' gestation: • Evidence of moderate benefits: decreased death, bronchopulmonary dysplasia, failed extubation and 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 extubation in infants < 34 weeks
Values	No uncertainty or variability about outcomes
Acceptability	Acceptable
Resources	Low to moderate
Feasibility	Probably feasible
Equity	Probably equitable