IMPROVING OUTCOMES OF VERY PRETERM INFANTS: EVIDENCE FOR PROPHYLACTIC CPAP AND CAFFEINE

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OUTLINE

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Introduction

- Preterm infants are babies born before 37 completed weeks of gestation (Extreme preterm, very preterm, moderate preterm & late preterm)

- Approximately 45% of all children under the age of five who die are newborns, and 60–80% of those newborns who die are preterm and/or small for gestational age.

- Preterm and LBW infants have a 2- to 10-fold higher risk of mortality than infants born at term and with normal birth weight.

- Despite substantial progress over the last 10 years, the survival, health, growth, and neurodevelopment of preterm and LBW infants are still of serious concerns in many countries.

Introduction 2

- Globally, 15 million babies are born preterm each year, representing 11% of all livebirths [1]
- Prevalence of preterm birth in Lagos (south-west, Nigeria) was 18.5% [2] 15.4% in Akure Ondo State [3]
- The very preterm birth rate was as high as 51.9% [4]

Vulnerability of very Preterms

- **CNS:** apnoeic attacks (AOP), IVH, HIE, more prone to Sz, ROP, deafness, CP
- **Respiratory**: RDS, pneumothorax, BPD, pulmonary hypoplasia, pulmonary haemorrhage
- **CVS**: proned to circulatory instability, PDA, persistent fetal circulation, pulmonary hypertension
- **GIT:** poor motility, NNEC, feeding problems (poor rooting, sucking, swallow reflexes),
- **Homeiostatic problems**: poor temperature regulation

Vulnerability of very Preterms 2

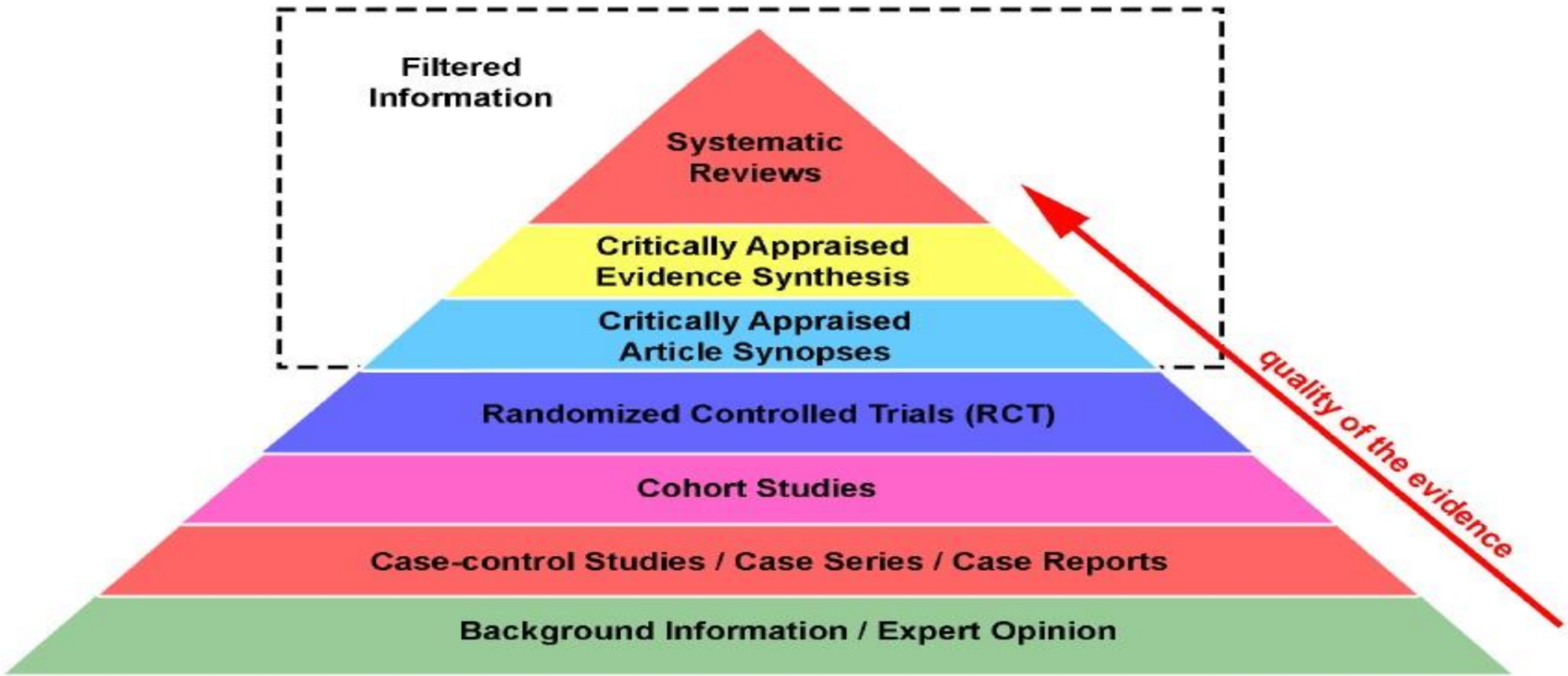
- GUS: early & late metabolic acidosis, loss of Na+ in urine, hyposthenuria
- Metabolic problems: hypoglycemia, hypocalcemia, etc
- Haematological problems: anaemia of prematurity, hyperbilirubinemia
- Low immunity; predisposition to sepsis due low levels of IgG, reduced chemotactic activity of the WBC, & reduced ability to engulf microbes
- Skin: they have relatively thin epidermis which is easily bruised

Evidence to decision framework

Processes needed to generate evidence-Based Practice

- Identifying priority questions and outcomes
- Retrieve information or evidence to answer the Question
- Critical assessment and synthesis of the evidence
- Integrate the evidence with own clinical practice
- Formulation of recommendations and write-up for dissemination of the information
- Planning for the dissemination, implementation, impact evaluation and updating of the recommendations

Levels of Evidence



Adapted from Strauss and Dartmouth Libraries, (2011).

DECIDE, GRADE AND GRADE-CERQual

- The DECIDE approach (**D**eveloping and **E**valuating **C**ommunication strategies to support **I**nformed **D**ecisions and practice based on **E**vidence) was used to guide the evidence search, evidence synthesis and judgements

- The DECIDE framework has nine core domains: benefits, harms, balance of effects, certainty, values, acceptability, resources, feasibility and equity.

- GRADE: **G**rading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuation for quantitative research

- GRADE-CERQual: **C**onfidence in the **E**vidence from **R**eviews of **Q**ualitative Research tool.

GRADE-CERQual: Confidence in the Evidence from Reviews of Qualitative Research tool.

- Has three domains : values, acceptability and feasibility,

- Each of them has four components:

➢ Methodological limitations of the individual studies;

➢ Adequacy of data;

➢ Coherence;

➢ and Relevance to the review question

Grading of the quality and certainty of the evidence

- The GRADE approach:

- Is used to appraise the quality and certainty of the quantitative evidence for each priority question.

- GRADE is a standard systematic approach for developing and presenting summaries of evidence for clinical practice recommendations.

- It uses standard tools, which are published online, including GRADE protocols and risk-of-bias tools for assessing randomized and non-randomized studies.

Grading of the quality and certainty of the evidence 2

- A GRADE Evidence-to-Decision framework is prepared for each quantitative outcome and the **certainty** of evidence is rated as “high”, “moderate”, “low” or “very low”.

- Standard criteria for baseline GRADE ratings are **that** RCTs provide “high-certainty” evidence **while** non-randomized trials and observational studies provide “low-certainty” evidence.

- This baseline certainty rating is then downgraded based on characteristics of the study design: risk of bias, inconsistency, imprecision, indirectness and publication bias

The Grade System

GRADE	DEFINITION
High ⊕⊕⊕⊕	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate ⊕⊕⊕○	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low ⊕⊕○○	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low ⊕○○○	Any estimate of effect is very uncertain.

Guyatt et al. BMJ 2008;336:924

Current Evidence for Continuous Positive Airway Pressure Use


Pumani
Diamedica Baby CPAP

CPAP

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

CPAP

- Several studies have been done in documenting the effectiveness of CPAP for the treatment of RDS
- And the systematic approach has been used to review these studies:

1. To compare use of CPAP **versus** use of Supplemental Oxygen
2. To compare Early **vs** Delayed CPAP
3. Immediate CPAP **vs** Supplemental Oxygen
4. Immediate CPAP **vs** Mechanical ventilation
5. Bubble CPAP **vs** other pressure sources

Any CPAP versus supplemental oxygen

- **Evidence of moderate benefits:**
- Decreased mortality (moderate-certainty evidence),
- Decreased mechanical ventilation (very-low-certainty evidence)
- Decreased “failed treatment”/ 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)

Any CPAP versus supplemental oxygen

Certainty assessment		Summary of findings				
Participants (studies) Follow-up	Overall certainty of evidence	No. of participants		Relative effect (95% CI)	Anticipated absolute effects	
		With supplemental oxygen	With any CPAP		Risk with supplemental oxygen	Risk difference with CPAP
Mortality by hospital discharge						
322 (5 RCTs)	⨁⨁⨁◯ Moderate	38/162 (23.5%)	20/160 (**12.5%**)	RR 0.53 (0.34 to 0.83)	235 per 1000	110 fewer per 1000 (from 155 fewer to 40 fewer)
Use of mechanical ventilation by hospital discharge						
233 (3 RCTs)	⨁◯◯◯ Very low	59/120 (49.2%)	38/113 (**33.6%**)	RR 0.72 (0.54 to 0.96)	492 per 1000	138 fewer per 1000 (from 226 fewer to 20 fewer)
Treatment failure (death or use of additional ventilatory support) by hospital discharge						
322 (5 RCTs)	⨁◯◯◯ Very low	84/162 (51.9%)	51/160 (**31.9%**)	RR 0.64 (0.50 to 0.82)	519 per 1000	187 fewer per 1000 (from 259 fewer to 93 fewer)
Pneumothorax by hospital discharge						
270 (4 RCTs)	⨁⨁◯◯ Low	8/139 (**5.8%**)	18/131 (13.7%)	RR 2.48 (1.16 to 5.30)	58 per 1000	85 more per 1000 (from 9 more to 247 more)
Bronchopulmonary dysplasia (oxygen dependency at 28 days)						
209 (2 RCTs)	⨁◯◯◯ Very low	6/108 (5.6%)	5/101 (5.0%)	RR 1.04 (0.35 to 3.13)	56 per 1000	2 more per 1000 (from 36 fewer to 118 more)

Source: Ho JJ, Subramaniam P, Davis PG. Continuous positive airway pressure (CPAP) for respiratory distress in preterm infants. Cochrane Database Syst Rev 2020

Early vs delayed CPAP

- **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 pneumothorax (low-certainty evidence)
- No evidence on other critical outcomes

Early versus delayed CPAP

Certainty assessment		Summary of findings				
Participants (studies) Follow-up	Overall certainty of evidence	No. of participants		Relative effect (95% CI)	Anticipated absolute effects	
		With delayed CPAP	With early CPAP		Risk with delayed CPAP	Risk difference with early CPAP
Mortality by hospital discharge						
119 (4 RCTs)	⨁⨁◯◯ Low	11/67 **(16.4%)**	9/52 (17.3%)	RR 0.93 (0.43 to 2.03)	164 per 1000	11 fewer per 1000 (from 94 fewer to 169 more)
Use of mechanical ventilation by hospital discharge						
119 (4 RCTs)	⨁◯◯◯ Very low	20/67 (29.9%)	13/52 (**25.0%**)	RR 0.77 (0.43 to 1.38)	299 per 1000	69 fewer per 1000 (from 170 fewer to 113 more)
Pneumothorax by hospital discharge						
98 (2 RCTs)	⨁⨁◯◯ Low	7/56 (**12.5%**)	6/42 (14.3%)	RR 1.09 (0.39 to 3.04)	125 per 1000	11 more per 1000 (from 76 fewer to 255 more)
Bronchopulmonary dysplasia at 36 weeks postmenstrual age						
29 (1 RCT)	⨁◯◯◯ Very low	1/17 (**5.9%**)	1/12 (8.3%)	RR 1.42 (0.10 to 20.49)	59 per 1000	25 more per 1000 (from 53 fewer to 1000 more)

Source: Ho JJ, Subramaniam P, Davis PG. Continuous positive airway pressure (CPAP) for respiratory distress in preterm infants. Cochrane Database Syst Rev 2020

CPAP immediately after birth

CPAP may be considered immediately after birth for very preterm infants (< 32 weeks' gestation), with or without respiratory distress.

Conditional recommendation

Low-certainty evidence

CPAP immediately after birth for very preterm infants vs supplemental oxygen (GA < 32 weeks)

- **Evidence of small benefits:**
- Decreased “failed treatment” (i.e. defined as recurrent apnoea, hypoxia, hypercarbia, increasing oxygen requirement or the need for mechanical ventilation),
- Decreased bronchopulmonary dysplasia (moderate-certainty evidence) and decreased pneumothorax (low-certainty evidence)
- **No evidence of harms**
- Evidence of little or no effect on mortality and intraventricular haemorrhage (moderate-certainty evidence)
- No evidence on other critical outcomes

Immediate CPAP versus supplemental oxygen

Certainty assessment		Summary of findings				
Participants (studies) Follow-up	Overall certainty of evidence	No. of participants		Relative effect (95% CI)	Anticipated absolute effects	
		With supplemental oxygen	With immediate CPAP		Risk with supplemental oxygen	Risk difference with immediate CPAP
Mortality by hospital discharge						
765 (4 RCTs)	⨁⨁⨁◯ Moderate	19/378 (5.0%)	22/387 (5.7%)	RR 1.09 (0.60 to 1.96)	50 per 1000	5 more per 1000 (from 20 fewer to 48 more)
Death or bronchopulmonary dysplasia by hospital discharge						
256 (1 RCT)	⨁⨁◯◯ Low	24/125 (19.2%)	18/131 (**13.7%**)	RR 0.69 (0.40 to 1.19)	192 per 1000	60 fewer per 1000 (from 115 fewer to 36 more)
Treatment failure by hospital discharge						
765 (4 RCTs)	⨁◯◯◯ Very low	148/378 (39.2%)	93/387 (**24.0%**)	RR 0.60 (0.49 to 0.74)	392 per 1000	157 fewer per 1000 (from 200 fewer to 102 fewer)

Source: Ho JJ, Subramaniam P, Davis PG. Continuous positive airway pressure (CPAP) for respiratory distress in preterm infants. Cochrane Database Syst Rev 2021

Immediate CPAP versus supplemental oxygen (Cont'd)

Bronchopulmonary dysplasia at 36 weeks postmenstrual age						
683 (3 RCTs)	⊕⊕⊕◯ Moderate	42/339 (12.4%)	34/344 **(9.9%)**	RR 0.76 (0.51 to 1.14)	124 per 1000	30 fewer per 1000 (from 61 fewer to 17 more)
Pneumothorax by hospital discharge						
568 (3 RCTs)	⊕⊕◯◯ Low	14/279 (5.0%)	11/289 (**3.8%**)	RR 0.75 (0.35 to 1.61)	50 per 1000	13 fewer per 1000 (from 33 fewer to 31 more)
Intraventricular haemorrhage grades 3 or 4 by hospital discharge						
486 (2 RCTs)	⊕⊕◯◯ Low	9/240 (3.8%)	9/246 (3.7%)	RR 0.96 (0.39 to 2.37)	38 per 1000	2 fewer per 1000 (from 23 fewer to 51 more)

Source: Ho JJ, Subramaniam P, Davis PG. Continuous positive airway pressure (CPAP) for respiratory distress in preterm infants. Cochrane Database Syst Rev 2021

CPAP immediately after birth for very preterm infants vs mechanical ventilation (< 32 weeks)

- **Evidence of moderate benefits:**
- Decreased “failed treatment” (i.e. defined as recurrent apnoea, hypoxia, hypercarbia, increasing oxygen requirement or the need for mechanical ventilation)
- Decreased bronchopulmonary dysplasia (moderate-certainty evidence)
- No evidence of harms
- Evidence of little or no effect on mortality (moderate-certainty evidence) pneumothorax (low-certainty evidence),
- Little or no effect on intraventricular haemorrhage (moderate-certainty evidence) and neurodevelopment (moderate-certainty evidence)
- No evidence on other critical outcomes

Immediate CPAP versus mechanical ventilation

Certainty assessment		Summary of findings				
Participants (studies) Follow-up	Overall certainty of evidence	No. of participants		Relative effect (95% CI)	Anticipated absolute effects	
		With mechanical ventilation	With immediate CPAP		Risk with mechanical ventilation	Risk difference with immediate CPAP
Mortality by hospital discharge						
2358 (3 RCTs)	⊕⊕⊕◯ Moderate	147/1165 (12.6%)	123/1193 (**10.3%**)	RR 0.82 (0.66 to 1.03)	126 per 1000	23 fewer per 1000 (from 43 fewer to 4 more)
Death or bronchopulmonary dysplasia by hospital discharge						
2358 (3 RCTs)	⊕⊕⊕◯ Moderate	547/1165 (47.0%)	495/1193 (**41.5%**)	RR 0.89 (0.81 to 0.97)	470 per 1000	52 fewer per 1000 (from 89 fewer to 14 fewer)
Treatment failure by hospital discharge						
1042 (2 RCTs)	⊕⊕⊕◯ Moderate	503/512 (98.2%)	257/530 (**48.5%**)	RR 0.49 (0.45 to 0.54)	982 per 1000	501 fewer per 1000 (from 540 fewer to 452 fewer)

Source: 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

Immediate CPAP versus mechanical ventilation (Cont'd)

Bronchopulmonary dysplasia at 36 weeks postmenstrual age						
2150 (3 RCTs)	⊕⊕⊕◯ Moderate	400/1051 (38.1%)	372/1099 (33.8%)	RR 0.89 (0.80 to 0.99)	381 per 1000	42 fewer per 1000 (from 76 fewer to 4 fewer)
Pneumothorax by hospital discharge						
2357 (3 RCTs)	⊕⊕◯◯ Low	67/1165 (5.8%)	85/1192 (7.1%)	RR 1.24 (0.91 to 1.69)	58 per 1000	14 more per 1000 (from 5 fewer to 40 more)
Intraventricular haemorrhage grades 3 or 4 by hospital discharge						
2301 (3 RCTs)	⊕⊕⊕◯ Moderate	112/1134 (9.9%)	125/1167 (10.7%)	RR 1.09 (0.86 to 1.39)	99 per 1000	9 more per 1000 (from 14 fewer to 39 more)
Neurodevelopmental impairment at 18 to 22 months corrected age						
976 (1 RCT)	⊕⊕⊕◯ Moderate	53/504 (10.5%)	45/472 (9.5%)	RR 0.91 (0.62 to 1.32)	105 per 1000	9 fewer per 1000 (from 40 fewer to 34 more)

Source: 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

CPAP pressure source

For preterm infants who need CPAP, bubble CPAP may be considered rather than other pressure sources (e.g. ventilator CPAP):

Conditional recommendation

Low-certainty evidence

Bubble CPAP vs other CPAP pressure sources

- **Evidence of small-to-moderate benefits:** decreased pneumothorax, decreased bronchopulmonary dysplasia and decreased failed treatment (low-certainty evidence)
- **Evidence of small harms:** increased nasal injury (i.e. defined as ulceration, bleeding, septal injury and/or scarring but excluding hyperaemia and erythema) (low-certainty evidence)
- Evidence of little or no effect on mortality (low-certainty evidence)
- No evidence on other critical outcomes

Bubble CPAP versus other pressure sources

Certainty assessment		Summary of findings				
Participants (studies) Follow-up	Overall certainty of evidence	No. of participants		Relative effect (95% CI)	Anticipated absolute effects	
		With other CPAP pressure sources	With bubble CPAP		Risk with other CPAP pressure sources	Risk difference with bubble CPAP
Mortality by hospital discharge						
1189 (10 RCTs)	⊕⊕◯◯ Low	46/592 (7.8%)	45/597 (7.5%)	RR 0.93 (0.64 to 1.36)	78 per 1000	5 fewer per 1000 (from 28 fewer to 28 more)
Treatment failure by hospital discharge						
1230 (13 RCTs)	⊕⊕◯◯ Low	132/614 (21.5%)	101/616 **(16.4%)**	RR 0.76 (0.60 to 0.95)	215 per 1000	52 fewer per 1000 (from 86 fewer to 11 fewer)
Pneumothorax by hospital discharge						
1340 (14 RCTs)	⊕⊕◯◯ Low	21/667 (3.1%)	15/673 **(2.2%)**	RR 0.73 (0.40 to 1.34)	31 per 1000	9 fewer per 1000 (from 19 fewer to 11 more)
Nasal injury by hospital discharge						
753 (8 RCTs)	⊕⊕◯◯ Low	18/377 **(4.8%)**	45/376 **(12.0%)**	RR 2.29 (1.37 to 3.82)	48 per 1000	62 more per 1000 (from 18 more to 135 more)
Bronchopulmonary dysplasia (oxygen dependency at 28 days)						
603 (7 RCTs)	⊕⊕◯◯ Low	49/293 (16.7%)	39/310 **(12.6%)**	RR 0.76 (0.53 to 1.10)	167 per 1000	40 fewer per 1000 (from 79 fewer to 17 more)

Source: Prakash R, De Paoli AG, Davis PG, Oddie SJ, McGuire W. Bubble devices versus other pressure sources for nasal continuous positive airway pressure in preterm infants. Cochrane Database of Syst Rev 2022

- **Current Evidence for Caffeine use**

Methylxanthines for treatment of apnoea

- **Caffeine is recommended for treatment of apnoea in preterm infants:**
- Strong recommendation
- Moderate-certainty evidence

Methylxanthine for treatment of apnoea in preterm infants vs placebo or no methylxanthine treatment

- **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

Methylxanthines versus placebo or no methylxanthine treatment – Apnoea Treatment

Certainty assessment		Summary of findings				
Participants (studies) Follow-up	Overall certainty of evidence	No. of participants		Relative effect (95% CI)	Anticipated absolute effects	
		With placebo or no methylxanthine treatment	With any methylxanthine		Risk with placebo or no methylxanthine treatment	Risk difference with any methylxanthine
Mortality at hospital discharge						
154 (3 RCTs)	⨁⨁◯◯ Low	6/73 (8.2%)	3/81 (**3.7%**)	RR 0.49 (0.14 to 1.78)	82 per 1000	42 fewer per 1000 (from 71 fewer to 64 more)
Apnoeic episodes by hospital discharge						
43 (1 RCT)	⨁◯◯◯ Very low	9/22 (40.9%)	6/21 (**28.6%**)	RR 0.70 (0.30 to 1.62)	409 per 1000	123 fewer per 1000 (from 286 fewer to 254 more)
Positive-pressure ventilation after institution of treatment by hospital discharge						
192 (5 RCTs)	⨁⨁◯◯ Low	11/92 (12.0%)	3/100 (**3.0%**)	RR 0.34 (0.12 to 0.97)	120 per 1000	79 fewer per 1000 (from 105 fewer to 4 fewer)
Supplemental oxygen at 36 weeks postmenstrual age						
805 (1 RCT)	⨁⨁⨁◯ Moderate	141/392 (36.0%)	107/413 (**25.9%**)	RR 0.72 (0.58 to 0.89)	360 per 1000	101 fewer per 1000 (from 151 fewer to 40 fewer)
Death or major neurodevelopmental disability at latest follow up (5 years)						
767 (1 RCT)	⨁⨁⨁◯ Moderate	153/367 (41.7%)	141/400 (**35.3%**)	RR 0.85 (0.71 to 1.01)	417 per 1000	63 fewer per 1000 (from 121 fewer to 4 more)

Source: Marques K, Roehr CC, Bruschettini M, Davis PG, Soll R. Methylxanthine for the prevention and treatment of apnea in preterm infants. Cochrane Database Syst Rev 2022

Methylxanthines for extubation

- **Caffeine is recommended for extubation of preterm infants born before 34 weeks' gestation:**
- Strong recommendation
- Moderate-certainty evidence

Methylxanthine for extubation in preterm infants vs placebo or no methylxanthine treatment (GA <34 wks)

- **Evidence of moderate benefits:**
- Decreased death, bronchopulmonary dysplasia, failed extubation and neurodevelopmental disability (moderate-certainty evidence)
- No evidence of harms

Methylxanthines versus placebo or no methylxanthine treatment – Extubation

Certainty assessment		Summary of findings				
Participants (studies) Follow-up	Overall certainty of evidence	No. of participants		Relative effect (95% CI)	Anticipated absolute effects	
		With placebo or no methylxanthine treatment	With any methylxanthine		Risk with placebo or no methylxanthine treatment	Risk difference with any methylxanthine
Death or major neurodevelopmental disability at 5 years						
676 (1 RCT)	⨁⨁⨁◯ Moderate	189/360 (52.5%)	141/316 **(44.6%)**	RR 0.85 (0.73 to 0.99)	525 per 1000	79 fewer per 1000 (from 142 fewer to 5 fewer)
Failed extubation by hospital discharge						
197 (6 RCTs)	⨁⨁⨁◯ Moderate	45/89 (50.6%)	27/108 (**25.0%**)	RR 0.48 (0.32 to 0.71)	506 per 1000	263 fewer per 1000 (from 344 fewer to 147 fewer)
Supplemental oxygen at 36 weeks postmenstrual age						
704 (2 RCTs)	⨁⨁⨁◯ Moderate	224/368 (60.9%)	165/336 (**49.1%**)	RR 0.81 (0.70 to 0.92)	609 per 1000	116 fewer per 1000 (from 183 fewer to 49 fewer)

Source: Marques K, Roehr CC, Bruschettini M, Davis PG, Soll R. Methylxanthine for the prevention and treatment of apnea in preterm infants. Cochrane Database Syst Rev 2022

Research Gaps

- Current series of systematic reviews revealed that there were limited data on the **:Given dose of caffeine, timing of initiation & duration of administration**. (RCTs are needed in these areas).

- Currently, the evidence for early CPAP is low, so more RCTs are needed to increase the quality of evidence.

- As NISONM members ; as we commence and continue use of early CPAP & caffeine we can also commence routine data gathering on our outcomes as observational data; it can contribute to National reviews and clinical practice.

Take Home Points

- CPAP is recommended. It is unethical to withhold CPAP from any baby that needs it.
- Immediate or at least Early CPAP for Preterm infants less than 32 weeks GA
- Bubble CPAP better than ventilator CPAP
- Caffeine has high recommendations compared to other methylxanthines
- **Research implication**: Many of the evidences are low to moderate certainty, therefore we need more data / research to increase the quality of evidence.

References

1. **Dieter Wolke.** Preterm birth: High vulnerability and no resiliency? Reflections on Van Lieshout et al. (2018). Journal of Child Psychology and Psychiatry; 59(11):1201-1204
2. **Oluwafemi RO**, Njokanma OF, Disu EA, Ogunlesi TA.(2013) Maternal factors in aetiology of small-for-gestational age among term Nigerian babies. *Niger J Paed* **40**(2):119-24.
3. **Oluwafemi** RO, Abiodun MT. (2016). Incidence and outcome of preterm deliveries in Mother and Child Hospital Akure, Southwestern, Nigeria. *Sri Lanka Journal of Child Health*, 45(1):11-17**.**
4. **Oluwafemi RO**, Abiodun MT. (2018). Growth patterns of preterm infants: A prospective study in an indigenous African population**. Sahel Med J, 21:181-8**. DOI:10.4103/smj.smj_14_18.
5. Ho JJ, Subramaniam P, Davis PG. Continuous positive airway pressure (CPAP) for respiratory distress in preterm infants. Cochrane Database Syst Rev 2020
6. Care of the Preterm/LBW. New WHO recommendations for care of preterm/LBW infants have the potential to transform maternal & newborn health care delivery. The Lancet 2022;400(10366):1828-1831
7. WHO recommendations: https://apps.who.int/iris/bitstream/handle/10665/363697/9789240058262-eng.pdf
8. Web annexes: https://apps.who.int/iris/bitstream/handle/10665/363698/9789240060043-eng.pdf
9. Evidence base. Web supplement: https://apps.who.int/iris/bitstream/handle/10665/363699/9789240060050-eng.pdf
10. Lancet Comment https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)02186-9/fulltext

THANK YOU FOR YOUR ATTENTION!