

## Supplementary appendix 2: Characteristics of the included studies

Author & Year Country	N	Study population	Weaning readiness criteria	Intervention		Weaning failure criteria	Primary Outcomes
				Experimental group	Control group		
Abdel-Hady et al 2011 <sup>[11]</sup> Ireland	60	Mean GA 31.1 $\pm$ 2.6 and 31.0 $\pm$ 2.4 weeks in both study groups CPAP	CPAP of 5 cmH <sub>2</sub> O and FiO <sub>2</sub> <0.30 <u>Clinically stable:</u> 1. Respiratory rate <60/min 2. No significant chest recession 3. No single apnea requiring bagging 4. Not more than 6 episodes of apnea requiring stimulation during the preceding 24h 5. Satisfactory arterial bloodgases (pH>7.25, PCO <sub>2</sub> <60 and base deficit <8)	<u>Stepdown strategy:</u> Switch to HFNC with 2L/min; first reduction of FiO <sub>2</sub> to 0.21, then reduction of flow with 0.5L/min every 6h until discontinuation	Reduction of FiO <sub>2</sub> on CPAP to 0.21, then stop CPAP	1. Decreased SpO <sub>2</sub> <87% despite increasing FiO <sub>2</sub> to max 0.60 2. Increased WOB 3. Increased frequency of apnea and BC (>6 requiring stimulation/24h) 4. Severe apnea or BC that required PPV 5. Worsening bloodgases (PaCO <sub>2</sub> >65mmHG or pH<7.2)	1. Duration of oxygen
Todd et al 2012 <sup>[7]</sup> Australia	154	Mean GA 26.9 $\pm$ 1.6, 27.3 $\pm$ 1.5 and 27.1 $\pm$ 1.4 weeks in the 3 groups CPAP with FiO <sub>2</sub> >0.25 for at least 24h	CPAP of 4-6 cmH <sub>2</sub> O and FiO <sub>2</sub> <0.25 <u>Clinically stable:</u> 1. Respiratory rate < 60/min 2. No significant chest recession 3. <3 episodes of self-reverting apneas (<20") and/ or BC (<100/min) and/or desaturation (<86%) in 1h for previous 6h 4. Average SpO <sub>2</sub> >86% most of the time or PaO <sub>2</sub> / TPao <sub>2</sub> >45mmHg 5. Not currently treated for PDA or sepsis 6. Tolerated time off CPAP during cares (>15min)	<u>Interval training (A):</u> CPAP 6h on and increasing periods of time off (starting with periods of 2h); when 16h off, trial stop CPAP  <u>Interval training (B):</u> Similar as group 1, but with support of LFNC at 0.5L/min during times off. When trial of stop CPAP, continuation of LFNC for 24h	Stop CPAP	1. Increased WOB with RR >75/min 2. Increased apnea and/or BC and/or desaturations >2 in 1 hour for the previous 6h period 3. Increased FiO <sub>2</sub> >0.25 to maintain SpO <sub>2</sub> >86% and/ or PaO <sub>2</sub> / TPao <sub>2</sub> >45mmHg 4. pH <7.2 5. PaCO <sub>2</sub> / TPaco <sub>2</sub> >65mmHg 6. Major apnea or BC requiring resuscitation	1. Time to wean off CPAP 2. CPAP duration
Rastogi et al 2013 <sup>[15]</sup> USA	56	Mean GA 28.12 $\pm$ 1.67 weeks CPAP (primary or post-extubation) for at least 48h	CPAP of 5 cmH <sub>2</sub> O and FiO <sub>2</sub> 0.21 <u>Clinically stable:</u> 1. No evidence of increased WOB 2. Stable for at least for 48h	<u>Interval training:</u> CPAP 3h on and 3h off for 48h; if tolerated, periods of CPAP off increased to 6h for the next 48h; if tolerated, stop CPAP	Stop CPAP		Success rate of the first trial to wean
O'Donnell et al 2013 <sup>[12]</sup> United Kingdom	78	Median GA 28 weeks (range 24-32) CPAP for at least 24h	CPAP of 3-5 cmH <sub>2</sub> O and FiO <sub>2</sub> 0.21	<u>Stepdown strategy:</u> Switch to LFNC (1L/min) with room air	Stop CPAP	1. >1 self-correcting apneic episode/hrs. 2. 1 apneic episode requiring moderate stimulation or bag-and-mask ventilation 3. Need for oxygen to maintain SpO <sub>2</sub> >85% 4. A score of 6-10 on the Silverman-Anderson Respiratory Scale	Weaning failure
Badiee et al 2015 <sup>[13]</sup> Iran	88	Mean GA 31.2 $\pm$ 2.6 weeks CPAP at 5 – 8cmH <sub>2</sub> O	CPAP of 5 cmH <sub>2</sub> O and FiO <sub>2</sub> <0.30 <u>Clinically stable:</u> 1. Lack of apnea 2. No signs of respiratory distress	<u>Stepdown strategy</u> Switch to HFNC 2L/min with FiO <sub>2</sub> 0.30; once FiO <sub>2</sub> weaned to 0.21, reduction of flow (0.5L/min every 1h) until flow of 0.5L/min; then stop HFNC	Continuation of CPAP 5 cmH <sub>2</sub> O and weaning of FiO <sub>2</sub> to 0.21; stop CPAP if stable for 6h	1. Increased WOB 2. Significant retraction 3. Increased apnea 4. Abnormal blood gases (2 samples with an interval of >2hrs with pH<7.2, pCO <sub>2</sub> >65mmHg and paO <sub>2</sub> <50mmHg with FiO <sub>2</sub> >60%)	Duration of oxygen requirement

**AcoRN:** Acute Care of at-Risk Newborn – **BC:** bradycardia – **CLD:** Chronic lung disease – **CPAP:** Continuous Positive Airway Pressure – **FiO<sub>2</sub>:** Fractional inspired oxygen concentration – **GA:** Gestational Age – **HFNC:** High flow nasal cannula – **IQR:** Inter quartile range – **kPa:** kiloPascal – **LFNC:** Low flow nasal cannula – **PaO<sub>2</sub>:** Partial arterial oxygen – **PaCO<sub>2</sub>:** Partial arterial carbon dioxide – **PCO<sub>2</sub>:** Partial carbon dioxide – **PDA:** Persistent ductus arteriosus – **PMA:** Post Menstrual Age – **PNA:** postnatal age – **PPV:** Positive pressure ventilation – **SpO<sub>2</sub>:** Pulse oximetry saturation – **TPaO<sub>2</sub>:** Transcutaneous partial arterial oxygen – **TPaCO<sub>2</sub>:** Transcutaneous partial arterial carbon dioxide – **WOB:** Work of breathing

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Tang et al 2015 <sup>[10]</sup> Australia	60	Mean GA 27.5 weeks (range 24.0 – 29.9) CPAP Mean PMA at enrollment 31 weeks (range 27 – 37)	CPAP <5 cmH <sub>2</sub> O and FiO <sub>2</sub> <0.25 <u>Clinically stable:</u> 1. Respiratory rate <60/min 2. No significant chest recession, 3. <3 episodes of apnea, BC, oxygen desaturation in 1h for the previous 12h, 4. SpO <sub>2</sub> >86% most of the time or PaO <sub>2</sub> >45mmHg and 5. Not currently treated for PDA or sepsis	1. <u>Stepdown strategy:</u> Switch to HFNC starting at flow 6L/min  2. <u>Interval training (A):</u> CPAP 6h alternated with ambient air/oxygen or LFNC during off periods; first progressive increase of time on air/LFNC and then decrease of time on CPAP  3. <u>Interval training (B):</u> Similar as A but CPAP 6h alternated with HFNC for 1h;	Stop CPAP to ambient air/oxygen (up to 25%) or to LFNC (<1L/min)	1. Increased WOB with respiratory rate >75 per minute, 2. Increased apnea and/or BC and/or desaturations >2 in 1h for the previous 6h period 3. FiO <sub>2</sub> >0.25 to maintain SpO <sub>2</sub> >86% and/or PaO <sub>2</sub> >45mmHg 4. pH <7.2, 5. PaCO <sub>2</sub> >65mmHg 6. Apnea or BC requiring resuscitation	1. CLD, 2. Days respiratory support (CPAP or HFNC or Oxygen) 3. Days of hospital stay 4. Days to achieve full suck feeds
Nair et al 2015 <sup>[16]</sup> Canada	30	Median GA 27 weeks (IQR 26-28) and 27 weeks (IQR 26-27) in both study groups Post-extubation CPAP for at least 72h	CPAP of 4 cmH <sub>2</sub> O	<u>Interval training:</u> Weaning schedule over 72h of CPAP alternated with LFNC (1L/min) with decreasing time on CPAP and increasing time on LFNC	Continuation of CPAP 4 cmH <sub>2</sub> O for 72h; then switch to LFNC (1L/min)	1. ACoRN respiratory score of 5 or more, or increase in previous score 2. FiO <sub>2</sub> >0.30 3. Acidosis (pH < 7.20) 4. Apnea with BC/desaturation requiring stimulation (>1/h) 5. Apnea requiring bag and mask ventilation	Successful weaning
Soonsawad et al 2016 <sup>[14]</sup> Thailand	101	Median GA 29 weeks (IQR 27-30) PNA at enrollment median 8 days (IQR 4-28) and 7.5 days (IQR 3-20) in both groups	CPAP ≤6 cmH <sub>2</sub> O and FiO <sub>2</sub> <0.30 <u>Clinically stable:</u> 1. Sat 88 - 93% 2. <3 Apnea or BC in 1h 3. No clinical signs of RDS 4. Being able to take off devices during nursing care 5. no clinical sign of hemodynamic significant PDA	<u>Stepdown strategy:</u> Switch to HFNC at 4 L/min (<1000g) or 5-6 L/min (>1000g) First decrease FiO <sub>2</sub> then decrease flow rate (1 L/min for 24h) until 3 L/min (>1000g) or 2 L/min (<1000g); then stop or switch to LFNC	<u>Gradual weaning</u> First decrease FiO <sub>2</sub> , then decrease CPAP pressure (1cmH <sub>2</sub> O for 24h) until 4 cmH <sub>2</sub> O; then stop or switch to LFNC	1. Increased WOB 2. Apnea or BC or desaturation >3 times within 1h during 6h under observation 3. Apnea requiring positive pressure ventilation 4. FiO <sub>2</sub> >0.6 to keep SpO <sub>2</sub> 88-93% 5. pH <7.25 or pCO <sub>2</sub> >65mmHg	Time to wean
Amataya et al 2017 <sup>[8]</sup> USA	68	Mean GA 28.7 ± 1.8 and 28.5 ± 1.9 weeks in both study groups CPAP (primary or post-extubation) for at least 48h Days to reach FiO <sub>2</sub> 0.21 on CPAP 5.6 ± 12.4 and 5.7 ± 12.6 days in both study groups	CPAP of 5cmH <sub>2</sub> O and FiO <sub>2</sub> 0.21 for at least 48h <u>Clinically stable:</u> 1. Normal WOB, no persistent tachypnea, no marked retractions 2. No apnea associated with BC or cyanosis with >2 episodes in 12h or >3 in 24h with at least one requiring bag and mask ventilation 3. SpO <sub>2</sub> >90% 4. Not currently treated for PDA or sepsis at the time of weaning 5. Tolerated time off CPAP during nursing cluster care up to 15 minutes or more	<u>Gradual weaning:</u> Weaning over 24h, i.e. reduction of CPAP pressure with 1 cmH <sub>2</sub> O every 8h, up to 3 cmH <sub>2</sub> O; then stop CPAP	Stop CPAP	1. Increased WOB: persistent tachypnea (>60 for 2h) and marked retractions 2. Apnea (cessation of respiration >20s) associated with BC or cyanosis with >2 episodes in 12h or >3 in 24h with at least one requiring bag and mask ventilation 3. FiO <sub>2</sub> >0.21 to maintain sat. >90% for over 2h in 24h 4. Abnormal blood gases (2 arterial samples >2h apart) with low pH<7.2, PaO <sub>2</sub> >65mmHg, PaO <sub>2</sub> <50mmHg	Success rate of the first trial of CPAP weaning

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Eze et al 2018 <sup>[17]</sup> USA	80	Mean GA 26.5 weeks (range 23.6-30.6) and 27.4 weeks (range 23.9-30.7) in both groups CPAP for at least 24h PNA at enrollment 37 days (range 3-100) and 31 days (range 3-67) in both groups	CPAP of 5-6 cmH <sub>2</sub> O and FiO <sub>2</sub> ≤0.30 for at least 24h And: 1. PMA ≥ 26 0/7 w 2. loaded with caffeine 3. stable respiratory assessment and Hb ≥ 8 g/dL	<u>Interval training</u> CPAP alternated with LFNC (< 2 L/min): 9h CPAP and 3h LFNC for 24h; then 6h CPAP and 6h LFNC for 24h; then 3h CPAP and 9h LFNC for 24h; then room air or LFNC after 24h of re-recruitment with CPAP	If CPAP 6 cmH <sub>2</sub> O: weaned to 5 cmH <sub>2</sub> O for 96h, then stop or switch to LFNC (≤ 2 L/min)  If CPAP 5 cmH <sub>2</sub> O: continued for 96h, then stop or switch to LFNC	1. Increased WOB 2. RR >70/min over 1h 3. FiO <sub>2</sub> >0.30 and/or >2 l/min via NC to keep SaO <sub>2</sub> levels over 86% 4. Apnea or BC requiring resuscitation, ranging from bag and mask ventilation to intubation	Successful wean off CPAP during the first trial (=total 7 days: 4 days weaning, 3 days observation) without failure
Yang et al 2018 <sup>[18]</sup> Taiwan	181	Mean GA 28.8 ± 2.4 weeks Positive pressure respiratory support for at least 24h Mean PMA at enrollment 33.3 ± 2.4 and 34.3 ± 2.4 weeks	CPAP of 5-7 cmH <sub>2</sub> O and FiO <sub>2</sub> <0.25 for 24h And: 1. weight > 1250 g 2. Hb >10 g/dL 3. No use of vasoactive or sedative agents	<u>Interval training (A)</u> CPAP alternated with LFNC oxygen at 0.2 L/min: increasing time off CPAP every 24h (4-8-12h); then stop CPAP  <u>Interval training (B)</u> CPAP alternated with LFNC air flow at 1.5 L/min: increasing time off CPAP every 24h (4-8-12h); then stop CPAP	Continuation of CPAP at 4 – 6 cmH <sub>2</sub> O for 5 days, then stop to room air or LFNC oxygen as needed	1. Increased WOB 2. Increase apnea and/or BC events and/or 2 desaturation periods in 1h for the previous 6h-period 3. Increase FiO <sub>2</sub> >0.25 to maintain SpO <sub>2</sub> >86% 4. pH <7.2 5. PaO <sub>2</sub> / TPaO <sub>2</sub> of >65mmHg 6. Major apnea or BC episode requiring resuscitation	1. Length of weaning duration 2. Body weight and post conceptional age of successful weaning
Jenssen et al 2018 <sup>[9]</sup> Denmark	354	Median GA 30 weeks (IQR 29-31) CPAP for at least 24h Median PMA at enrollment 32 weeks (IQR 31-32)	CPAP <8 cmH <sub>2</sub> O and FiO <sub>2</sub> <0.30 And: 1. PMA ≥ 29 0/7 weeks 2. Respiratory rate <70/min 3. <3 episodes of BC or desaturations in 24hrs 4. Tolerate CPAP off during nursing procedures (up to 15 min)	<u>Gradual weaning group</u> Reduction of CPAP pressure with 1 cmH <sub>2</sub> O every day, down to 4 cmH <sub>2</sub> O; then stop CPAP	Stop CPAP	1. RR >70 per minute 2. Difficult breathing with retractions 3. Increased oxygen requirement by more than 10% 4. >3 episodes of oxygen sat <70% or heart rate <70 BPM in 24hrs 5. Major apnea or BC requiring resuscitation 6. TCO <sub>2</sub> >2kPa starting point	Weight gain velocity (g/kg/d)
Mohammadzadeh 2019 <sup>[19]</sup> Iran	62	Mean GA 30.5 ± 2.6 and 30.1 ± 1.8 weeks in both study groups CPAP (primary for RDS or post-extubation) for at least 24h Mean PMA at enrollment 31.0 ± 2.4 and 31.1 ± 3.7 weeks	CPAP of 5 cmH <sub>2</sub> O and FiO <sub>2</sub> 0.21 for 24h <u>Clinically stable:</u> 1. RR <60/min 2. Absence of diaphragmatic or sternal retraction 3. <6 episodes of apnea and BC within 24h 4. Absence of apnea requiring PPV 5. SpO <sub>2</sub> most of the time >86% 6. No PDA or sepsis 7. Tolerability of separation from CPAP for nursing care episodes (>15 min.)	<u>Interval training:</u> CPAP (ON) alternated with room air or ambient oxygen (OFF): increasing time off CPAP every 24h (4h - 8h - 12h); then stop CPAP	Stop CPAP	1. SpO <sub>2</sub> <87% and increased oxygen need 0.60 2. Increased WOB 3. >6 episodes of apnea and BC within 24h improving with slight stimulation 4. 1 episode of severe apnea or BC requiring PPV 5. Arterial pH<7.2 or PCO <sub>2</sub> >65mmHg	Successful CPAP weaning at first attempt

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