Online Supplement

The efficacy and safety of high flow nasal oxygen as respiratory support for children up to 24 months of age with bronchiolitis on a ward setting: A systematic review and meta-analyses

Carwyn Dafydd,*[1] Benjamin J Saunders,*[1] Sarah J Kotecha,[2] Martin O Edwards[1,2]
*Joint first authors
[1]Department of Child Health, University Hospital of Wales, Cardiff, United Kingdom
[2]Department of Child Health, School of Medicine, Cardiff University, Cardiff, United Kingdom

Table 1: Characteristics of included studies

STUDY	QUALITY SCORE	OBJECTIVE	SETTING	STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOMES
Abboud 2015 [1] Country not given paper	14	Determine whether initial therapy with HFNC improves respiratory symptoms, and to identify factors associated with failure of HFNC resulting in intubation.	PICU	RCT Retrospective analysis to determine factors associated with HFNC failure Single site	36 infants < 12 months (gender not stated) on HFNC (at least an hour of therapy to be included)	15 infants on SOT via nasal cannula (3 excluded as changed to HFNC before an hour of therapy)	1. Treatment failure: progression to HFNC (NC group only), CPAP or intubation – SOT group: 7 (58%) failed; 4 moved to HFHH after 1hr, 1 to CPAP, and 2 were intubated. HFNC group: 25% failed; 5 required CPAP and 4 intubation (p=0.073) - 2. PICU LOS - PICU LOS was tripled in pts who failed (184 ±74 vs. 60±41hr, p<0.01 3. Changes in physiological parameters: RR, work of breathing (WOB), capillary pH and pCO2, desaturations, and grunting pre and 1hr post therapy initiation - pH and pCO2 improved in the NC group pre vs. post therapy, but RR, WOB, desaturations and grunting did not change. In contrast, all variables improved in the HFHH group (p<0.01)
Bueno Campaña et al 2013 [2] Spain	15	Demonstrate that HFNC is superior to SOT with inhaled hypertonic saline solution (HSS)	Ward	RCT HFNC vs SOT+HSS No crossover 2 sites	32 infants <6 months (11 male) HFNC, 6-8l/min	42 infants <6 months (22 male) 2 mL of nebulised HSS(3%) 4hrly, conventional nasal prong	1. Respiratory Assessment Change Score – Respiratory Distress Assessment Instrument score before and after treatment, plus a value of +1 for each 10% improvement (decrease) in the post-treatment RR or a value of −1 for each 10% worsening (increase) in RR at time intervals - no difference (p =0.24) 2. Comfort score - no difference (p=0.7)

		in moderate bronchiolitis				oxygen up to 3l/min	3. LOS (days) - HFNC 5 vs SOT+HSS 4.5 4. Admission to PICU (5 in each group)
Cesar et al 2020 [3] Brazil	14	Pilot study – comparing CPAP to HNFC for critical bronchiolitis in PICU	PICU	RCT Single site No crossover	34 infants <9 months (gender not given), HFNC up to 8l/min	28 infants <9 months , 6cm CPAP via nasal mask	1. Treatment failure: defined as the need to escalate support to noninvasive bilevel pressure ventilation, or endotracheal intubation - 10 (35.7%) CPAP vs 13 (38.2%) HFNC (p=0.952) 2. Duration of NIV (2 vs 3 days, p=0.316) 3. PICU LOS (5 vs 5 days, p=0.459) 4. Hospital LOS (8 vs 9 days, p=0.95) 5. Intubation (3 (10.7%) vs 7 (20%) , p=0.49
Chen et al 2019[4] USA	15	Pilot study – comparing HFNC to SOT for moderate bronchiolitis	Ward	RCT Single site No crossover	16 patients ≤24 months (69% male) receiving HFNC	16 patients ≤24 months (56% male) receiving SOT	1. Change in RDAI over time (no difference, p=0.56), change in RR over time (no difference, p=0.38) 2. LOS (days) – no difference: HFNC 4.56, SOT 4.44 (p=0.92) 3. Duration of oxygen requirement (hours) – no difference HFNC 72.11, SOT 60.02 (p=0.59)
Durand et al 2020[5] France	17	HFNC vs SOT for moderate bronchiolitis	Ward/ED	RCT Multicentre No crossover	133 infants aged 7 days to 6 months (61% male) receiving HFNC at 3L/kg/min	135 infants aged 7 days to 6 months (52% male) receiving SOT up to 2L/min	1. Treatment failure requiring escalation of respiratory support within 7 days (objective criteria – FiO2 >40%, refractory apnoea episodes or worsening PaCO2 or m-WCAS score compared to baseline) – no difference HFNC 19 (14%) vs SOT 27 (20%) (OR 0.66 (0.35–1.26))

							2. PICU transfer – HFNC 21 (15%) vs SOT 26 (19%) (p=0.45) 3. Total LOS – HFNC 4.4±2.4 vs SOT 3.8±2.7 4. Duration of oxygen therapy (days) - HFNC 1.7±1.7 vs SOT 2.5±2 5. Length of nutritional support (days) HFNC 2.9±2.1 vs SOT 2.4±2.2 6. Adverse events – 3 pneumothroaces in HFNC group 7. Assessment of short-term respiratory status (at hours 1, 6 and 12)
Ergul et al 2018 [6] Turkey	16	OxyMask vs HFNC in patients with moderate or severe bronchiolitis.	PICU	RCT Single site No crossover	30 patients aged 1-24 months (19 male) (HFNC at 1 L/kg/min, up to 20 L/min.	30 patients aged 1-24 months (19 male) O2 (10–15 L/min) via an OxyMask	1. Treatment failure rate: No change or an increase in RR compared to baseline, no change or an increase in HR compared to baseline or persistence of low SpO2 (< 92%) adequate oxygen flow rate and FiO2 in the HFNC group/oxygen flow rate of 15 L/min in the mask group. - HFNC 0 failures, vs 7 in Oxymask (p=0.01) 2. Time to weaning off oxygen (h) HFNC 56 vs Mask 96 p< 0.001 3. Length of ICU stay (days) HFNC 3 vs Mask 4 p< 0.001

							4. Length of hospital stay (days) HFNC 4 (3/4) vs Mask 5 (4/6) p< 0.001 5. Clinical and laboratory parameters
Franklin et al 2018 [7] Australia/New Zealand	17	Whether early HFNC on wards and EDs prevents treatment failure resulting in escalation to PICU in moderate bronchiolitis	Ward/ED	RCT Multi-site Crossover from SOT to HFNC if treatment failure, but not vice versa	739 infants <12 months (477 male) HFNC up to 2 l/kg/min	733 infants <12 months (448 male) SOT up to 2 l/min	1. Primary treatment failure, defined as 3 out of: Increase or no decrease in HR >5bpm, Increase or no decrease in RR >5bpm, FiO2 over 40% on HFNC or O2 >2l/min to maintain sats >92% or 94%, Hospital early warning score triggered review and escalation of care OR Clinician decision to escalate for other reasons HFNC 87 (12%) vs SOT 167 (23%) of 733 p<0.001 NB. Of 167 infants crossing over from SOT to HFNC, 102 (61%) responded to HFNC rescue therapy; 65 (39%) did not, transferred to ICU Secondary outcomes: 2. Proportion of infants who were transferred to ICU - HFNC: 87 (12%) SOT 65 (9%) p=0.08 (but SOT is after attempted rescue HFNC) 3. Duration of oxygen therapy (days, mean±SD) – HFNC 1.87±2.09 vs SOT 1.81±2.18 4. Duration of ICU stay - HFNC 2.72±2.31 vs SOT 2.63±1.70

							5. Duration of hospital stay - HFNC 2.94±2.73 vs SOT 3.12±2.43 6. Intubation rate: 8 HFNC vs 4 SOT (p=0.39) 7. No adverse events
Hathorn 2014 [8]	15	HFNC vs SOT	Ward	Prospective open RCT	36 patients <18 months (15 male) HFNC oxygen at 8 l/min	36 patients <18 months (15 male) low flow oxygen (up to 2 l/min)	Validated composite clinical score (modified Tal) at 3h intervals - no figures given. No improvement in time to resolution of respiratory distress or oxygen requirement in patients receiving HFNC oxygen therapy. Trend towards lower clinical scores in the first 3 h following initiation of treatment in the intervention group. No adverse effects from HFNC therapy, and it was found to be safe in a ward environment.
Kefala-Agoropoulou et al 2015 [9] Country not stated	11	To test the hypothesis that HFNC may reduce PICU transfers as compared with standard treatment	Ward/ED	Not stated – "randomised method to determine treatment modality"	"Group 1" HFNC 2l/kg/min	"Group 2" low flow O2 up to 2l/min	"A severity assessment respiratory distress score, a detailed medical history and an O2 administration rapport are obtained. Patients who suffer severe respiratory distress and those who fail to stabilise with standard treatment are rescued by HFNC" "During the first 4 month period of the study (28/9/2014- 12/2/2015), 4 patients from group 2 were rescued by HFNC. There was only a 2 month old premature baby of a twin gestation, from group 1 transferred to PICU from PED due to RSV bronchiolitis. During the same period of the last year when no HFNC was available there

							were 12 PICU transfers due to respiratory distress 9/12 from the PW due to bronchiolitis"
Kepreotes et al [10]	15	HFNC vs SOT for moderate bronchiolitis	Ward/ED	RCT Single centre Crossover from SOT to HFNC if treatment failure, but not vice versa	101 patients <24 months (63 male) on HFNC at 1L/kg/min in 1:1 with O2	101 patients <24 months (75 male) on SOT – up to 2l/min	1. Time to wean off O2 therapy - 24 hours SOT, 20 hours for HFNC (p=0.61) Secondary outcomes: 2. Time to treatment failure, defined as critically abnormal observations or clinician decision: HR=0.29; 95%CI: 0.15 to 0.55; (p<0.001) 3. Treatment failure proportion: HFNC 14.9% versus SOT 32.7% p<0.005 NB. Of 32 infants crossing over from SOT to HFNC, 19 (59%) avoided transfer to PICU. 4. Adverse events: 4 in HFNC, 2 in SOT arm 5. Transfer to ICU – 12 in HFNC, 14 in SOT (p=0.41)
Martinez 2019 [11] Spain	15	Discover ideal initial HF flow rate in moderate bronchiolitis	Ward	Quasi randomised trial of 15l/min vs 10l/min HFNC. Crossover from 10-15	26 infants on 10l/min HFNC	31 infants on 15l/min HFNC	1. Days on HFNC – (10l/min vs 15l/min) 4 vs 4 2. Total LOS - 8 vs 8 3. PICU admission - 11 vs 5 4. Failure of therapy - 22 vs 5 5. Changes in HR and RR over time
Mayfield 2014[12]	14	To obtain data on the safety and clinical impact of	Ward	Prospective pilot study - control group	61 infants <12 months (39	33 infants <12 months (19 male),	1. Recording of adverse events – 0 in either group

Australia		managing infants with bronchiolitis on the ward with high-flow nasal cannula (HFNC) treatment.		retrospectively identified	male), HFNC 2l/kg/min	standard low-flow subnasal oxygen	2. Change in physiological parameters including heart rate (HR), respiratory rate (RR), SpO2, temperature and a respiratory score for WOB 3. PICU admission rates – 8 (13%) of HFNC group, 10 (31%) of SOT group (OR 4.086, 95% CI 1.0–8.2; P = 0.043) 4. Hospital LOS – median 92h in both groups 5. Length of treatment (HFNC or SOT – PICU admissions (non-responders) vs patients remaining on ward (responders)
Milani et al 2015 [13] Italy	16	Clinical outcomes for HFNC vs SOT for moderate-severe bronchiolitis	Ward	Observational study	18 infants <12 months (8 male) treated with HFNC (L/min = 8 mL/kg x respiratory rate x 0.3)	18 infants <12 months (10 male) treated with SOT	1. Physiological parameters over time – (RR, respiratory effort, ability to feed) – favoured HFNC (p = 0.026) 2. Total LOS - HFNC 6 days vs SOT 9 days (p<0.005) 3. Total LOO - HFNC 4 days vs SOT 6 days (p<0.005) 4. Adverse events – 0 in either group 5. Treatment failure (PICU admission) – 2 in each group
Milesi et al [14] 2017	16	HFNC vs nCPAP for the initial respiratory management in	PICU	Multicentre RCT, HFNC vs nCPAP, crossover of	71 infants <6 months (gender not given) treated with	71 infants <6 months (gender not given) treated with	1. Treatment failure, defined as (1) a 1-point increase in mWCAS compared with baseline; (2) RR rise >10 bpm compared with baseline, with RR >60 bpm; (3) a 1-point increase in the EDIN

France		young infants with moderate to severe bronchiolitis		patients with treatment failure	HFNC at 2L/kg/min	nCPAP at 7cm H_2O	score compared with baseline, with EDIN >4 despite the use of hydroxyzine (1 mg/kg); and (4) more than two severe apnea episodes per hour (i.e., requiring bag and mask ventilation), despite a loading dose of caffeine (20 mg/kg) after the first apnea: nCPAP 22 vs HFNC 36 (p=0.001) 2. Success rate after crossover: Of 22 CPAP failures, 18 succeeded on HFNC, of 36 HFNC failures, 26 succeeded on CPAP 3. Intubation: CPAP 3 vs HFNC 5 (p=0.72) 4. PICU LOS: CPAP 7.5 days vs HFNC 6.2 days (p=0.44) 5. Serious adverse events: 0 6. Occurrence of skin lesions: CPAP 6 vs HFNC 2 (p=0.27)
Milesi et al 2018 [15] France	17	3L/kg/min vs 2L/kg/min HFNC for the management of moderate to severe bronchiolitis	PICU	Multicentre RCT	144 infants <6 months (86 male) on HFNC 3L/kg/min	142 infants <6 months (84 male) on HFNC 2L/kg/min	1. Treatment failure, defined as (Milesi et al 2017): 38.7% (2L) vs. 38.9% (3L); p=0.98 2. Exact timing and causes of failures 3. Failure management in the two groups 4. Early protocol cessation for dramatic improvement 5. Intubation rate: 2.8% (2L) vs. 6.9% (3L) p=0.17 6. HFNC-associated skin lesions: 1.4% between both groups

							7. PICU LOS: 6.4 (3L) vs. 5.3 (2L) days, p=0.048 8. Serious adverse events (air leak syndrome and death): 0
Murphy 2020 [16] South Africa	13	HFNC vs SOT for the management of moderate/severe bronchiolitis outside the ICU, in a setting with limited PICU resources	Paediatric "high-care ward" – no on site PICU	Single Centre RCT	15 infants (gender not stated) between 1 month and 2 years treated with HFNC at 2L/kg/min	13 infants (gender not stated) treated with SOT by nasal cannula at 2 L/min OR Venturi 40% facemask at 8 L/min OR 100% oxygen via an oxygen flowmeter without a blender	1. Change in Tal score at time intervals: Sig improvement in Tal score for HFNC group - HFNC 7(3) to 3(4) p=0.04 vs SOT 7(2) to 5(10) p=0.69 2. Comparison of HR at time intervals (significant improvement in HR at 1hr for HFNC compared to SOT – p=0.005 3. Duration of oxygen support (days) HFNC 5.5 (3.25 - 6.75) vs SOT 6 (7) p=0.7 4. LOS of survivors (days) HFNC 8 (4) vs 8 (9) p=0.44 5. Intubation rate, HFNC 3 (20%) vs 6 (46%) p=0.139
O'Brien 2018[17] USA	9	Investigate use of a weaning protocol for HFNC in patients with bronchiolitis	PICU	Single centre before and after study	55 infants <12 months treated after protocol implementation (gender not stated)	59 infants <12 months treated before protocol implementation (gender not stated)	1. PICU LOS: 1.9 days post vs 2.8 days pre protocol (p=0.02) 2. Hospital LOS: No difference 3. PRISM 3 score: not stated (abstract only) 4. Length of intubation or noninvasive ventilation: not stated 5. Duration of HHFNC: 29 hours post vs 46 hours pre protocol (p=0.002)

							6. Rate of failure of therapy: 15% both pre and post protocol
Ramnarayan et al 2018 [18] UK	14	Pilot study to explore feasibility of a HFNC vs CPAP RCT in PICU for step up (Group A) and step down (Group B) respiratory support	PICU	Pragmatic, open, multi-centre pilot RCT	HFNC (flow rates not given) Group A: 2/16 had bronchiolitis, age of subgroup not stated) Group B: 8/41 had bronchiolitis	CPAP Group A: 4/13 had bronchiolitis Group B: 11/41 had bronchiolitis	1. Adverse events 2. Treatment crossover 3. Intubation rates 4. Length of ventilation [Subgroup data for bronchiolitis not available at time of writing]
Sarkar et al 2018 [19] India	15	CPAP vs HFNC in severe bronchiolitis	PICU	Single centre, parallel group, open label, and randomised pilot study	15 infants aged 28 days to 12 months (4:11 M:F) on HFNC 2 L/kg/min for infants under 10 kg and for infants >10 kg 2 L/kg/min for the first 10 kg + 0.5 L/kg/min for each kg above	16 infants aged 28 days to 12 months (10:6 M:F) on nCPAP	1. Improvements in (i) SpO2 % (ii) heart rate (HR); respiratory rate; (iii) partial pressure of carbon dioxide; (iv) partial pressure of oxygen; (v) RDAI score: All the parameters improved steadily in both groups, no sig difference 2. COMFORT Score: favoured HFNC ($p<0.003$) 3. Total duration of noninvasive ventilation support: CPAP 3.8 ± 0.80 days vs HFNC 3.6 ± 0.63 days ($p=0.33$) 4. PICU LOS: CPAP 5 ± 1.788 days vs HFNC 5 ± 1.6 days ($p=0.105$) 5. Incidence of nasal injury: HFNC 46.7% vs. CPAP 75% ($p=0.21$)

							6. NIV failure and intubation: 1 in each group (p=0.29) 7. Major adverse events – none recorded
Sood et al 2012 [20] USA	11	SOT vs HFNC at 4L/min vs HFNC at 8L/min for bronchiolitis	PICU	Multi-centre, prospective study	Numbers not stated: "Infants" Randomised to 1. SOT 2.HFNC at 4L/min 3.HFNC at 8L/min		1. Changes in physiological parameters: pre/post therapy blood gases, respiratory rates (RR), validated work of breathing (WOB) scores: no sig difference in change in blood gases, better WOB for HNC vs SOT at 1hr and 24hrs (p=0.001), better RR at 1hr and 24hrs for HFNC vs SOT (p=0.01) 2. LOO: no difference 3. Hospital LOS: not stated 4. Treatment failure (no definition given, no numbers stated – "less in HFNC" (p<0.05)
Turë et al 2020[21] Turkey	15	HFNC vs SOT (delivered via non-rebreathe mask with reservoir) for moderate to severe bronchiolitis	Ward	Single centre RCT Crossover from SOT for HFNC	37 patients under 2 years (54% male) treated with HFNC at 2 L/kg/min for patients weighing < 10 kg and 1 L/kg/min for	38 patients under 2 years (53% male) treated with oxygen at 10-15 L/min administered via an NFM with reservoir	1. Time to a reduction in cardiac apex beat by 20% (hour) SOT 8.26 ±6.4 vs HFNC 2.81± 1.8 (p=0.001) 2. Time to a reduction in respiration rate by 20% (hour) SOT 12.65 ±8.18 vs HFNC 5.37 ±4.54 (p=0.001) 3. Time to normalization of cardiac apex beat and respiration rate (hour) SOT 19.31 ±10.44 vs HFNC 10.13 ±7.82 (p=0.002)

					those weighing > 10 kg		4. Duration of oxygen therapy (days) SOT 1.05 ±0.44 vs HFNC 0.71 ±0.39 (p=0.001) 5. LOS (days) SOT 1.84 ±0.65 vs HFNC 1.29 ±0.49 (p=0.001) 6. PICU transfer – SOT 2, HFNC 0 (p>0.05)
Vahlkvist et al 2020[22] Denmark	15	CPAP vs HFNC for	Ward	Multicentre RCT Crossover	22 children <2 years (68% male) with bronchiolitis needing respiratory support as assessed by the pediatrician in charge, treated with HFNC at 2L/kg/min up to 15L/min	28 children <2 years (53% male) with bronchiolitis needing respiratory support as assessed by the pediatrician in charge, treated with CPAP	1. Changes in physiological parameters (RR, pCO2, FiO2, and m-WCAS) all declined during the first 48 h of treatment. No significant difference. 2. Neonatal Infant Pain Score (NIPS) overall lower in HFNC group (p<0.05) 3. Duration of NIV support (days) - CPAP 2.9 (0.25–10) HFNC 3.9 (1.1–8) 4. LOS – numbers not stated, no sig difference 5. Treatment failure (assessed by physician in charge): HFNC 2 switched to CPAP (disease progression) vs CPAP 4 (2 poor tolerance, switched to HFNC), 2 transferred to PICU 6. PICU transfer: HFNC 0 vs CPAP 2 (7.1%)
Yurtseven et al 2019 [23] Turkey	16	HFNC at 1L/kg/min vs 2L/kg/min for severe bronchiolitis	ED	Prospective clinical study	88 infants <24 months (63 male) on HFNC at 1L/kg/min	80 infants <24 months (60 male) on HFNC at 2L/kg/min	1. Treatment failure, defined as: “a clinical escalation in respiratory status.” 11.4% 1L group vs 10% 2L group (p=0.775) 2. Change in physiological parameters: Reductions in RR (p<0.001), and HR (p<0.001), and increase in SpO2 (p<0.001) were significantly

							higher in the 1L/kg/min group than the 2-L/kg/min group 4. Rates of weaning: At the 2nd hour of the therapy, the weaning rate was higher in the 1L group than the 2L group (53.4% vs 35%; HR 1.39 p=0.017 5. Intubation: no significant difference – 13 (7.7%) overall 6. ICU admission: no significant difference - 28 (16.7%) overall

Figure 1 online supplement Comparison of high-flow nasal cannula (HFNC) vs SOT outcome: rates of intubation

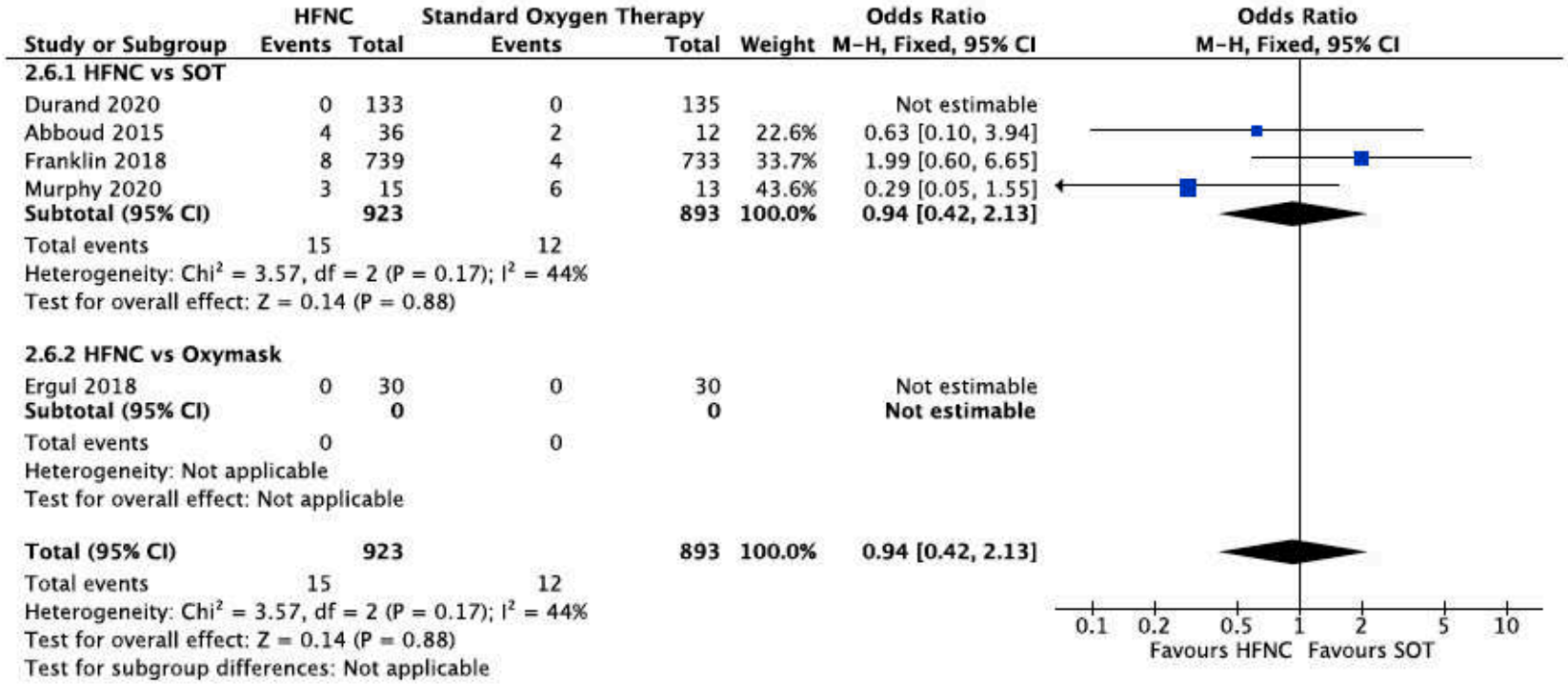


Figure 2 online supplement Comparison of high-flow nasal cannula (HFNC) vs CPAP outcome: rates of intubation

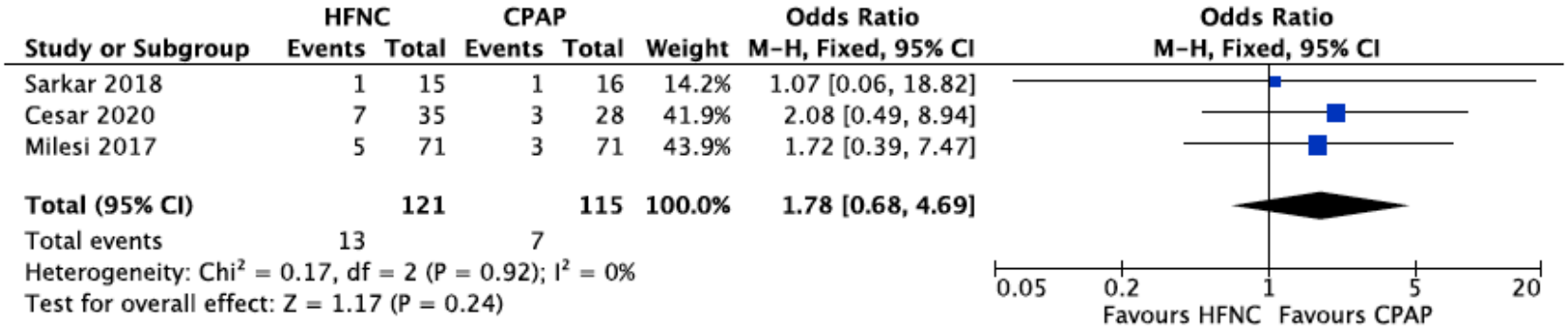


Figure 3 online supplement Comparison of high-flow nasal cannula (HFNC) vs SOT and Oxymask outcome: total oxygen therapy in days

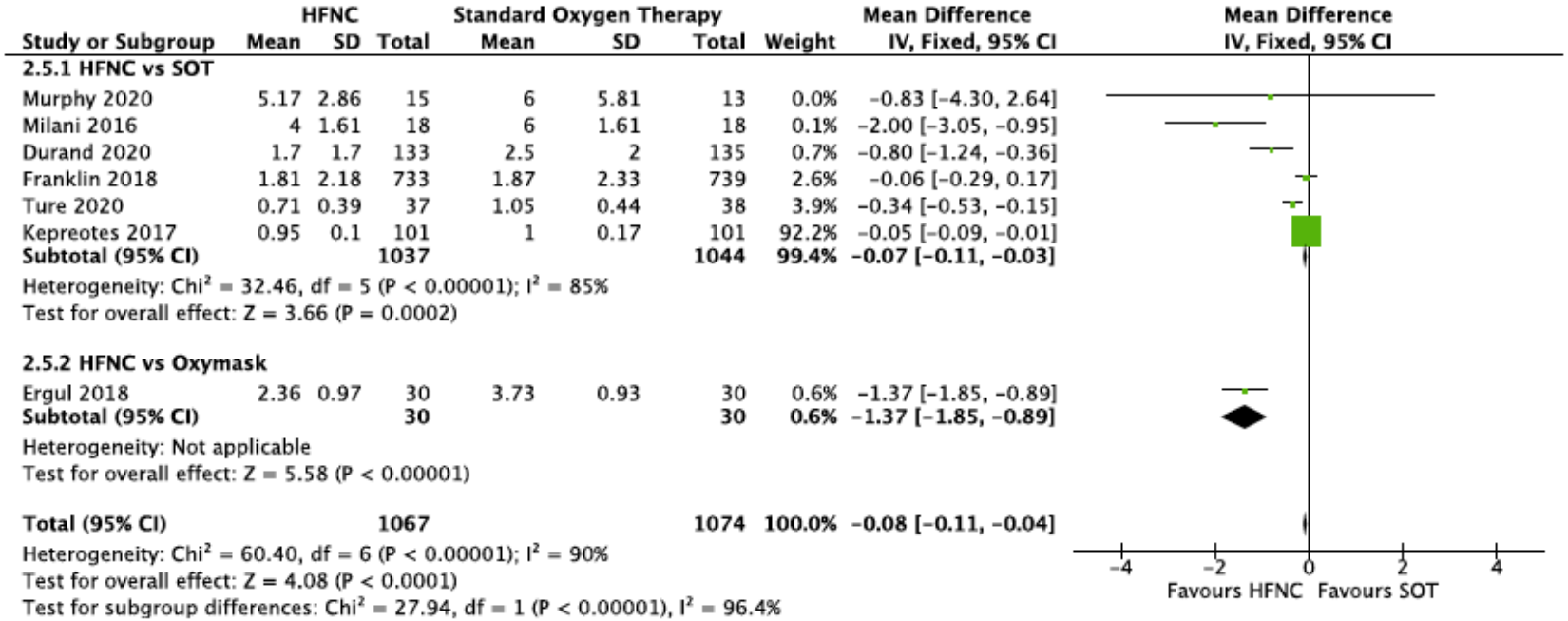
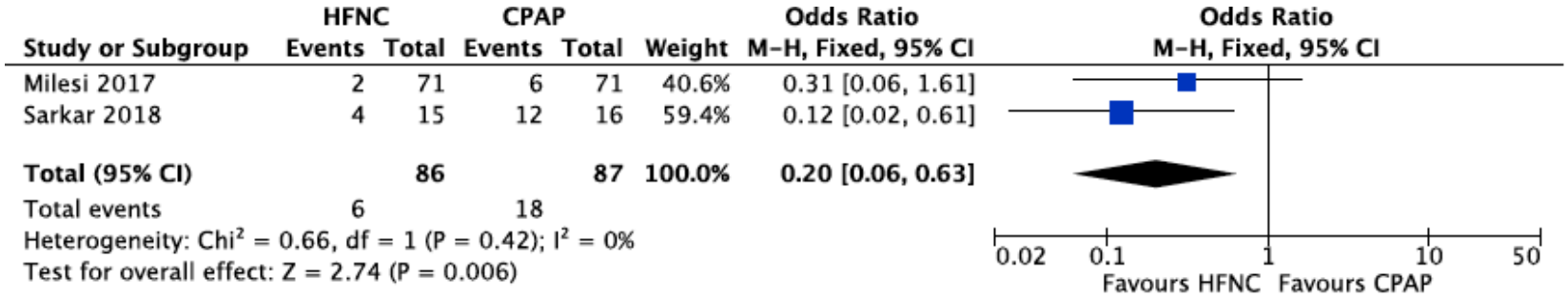


Figure 4 online supplement Comparison of high-flow nasal cannula (HFNC) vs CPAP outcome: adverse effects



Review Questions

1. To assess the efficacy and safety of High Flow Therapy Nasal Cannula (HFT) as respiratory support for children up to 24 months of age with bronchiolitis on a ward setting compared to a HDU setting.

2. To collate clinical recommendations on use including weaning.

Outcome of interest

Any death in hospital Death before discharge

Any air leak (pneumothorax, PIE)

Failure of therapy (any pre-defined) within 3 days Failure of therapy (any pre-defined) within 7 days Nasal trauma

Patient Comfort (assessed by carers/parents) Length of stay

Length of oxygen supplementation Transfer to ICU

Incidence of intubation

Length of non-invasive ventilation

Respiratory rate, heart rate, PaCO2 of carbon dioxide. PaO2 of oxygen and pulse oxygen saturation

Adverse events

Secondary question

Analysis for infants up to 12months of age only

Study population

Studies that include children up to 24 months of age with bronchiolitis in any country. Studies published from any year and in any language.

Inclusion Criteria

1) Prospective, randomised OR quasi randomised controlled trials.

2) Trials involve infants or children up to 24 months of age with bronchiolitis. Preterm infants will be included if they ae re-admitted with bronchiolitis. No trials will be excluded based on diagnosis of disease or condition in the infants.

3) At least one or more of the relevant review outcomes (see below) reported in the results or recommendations given.

4) Patients with bronchiolitis as diagnosed by BTS or ATS guidelines or doctor diagnosed.

Search strategy

A search strategy was developed for electronic databases using the keywords and MeSH headings below. The search strategy was tested for citations on the OVID Medline database 1950-2019.

The search strategy will be modified to search rest of the bibliographic databases. In addition, a range of 'snowballing' techniques will be used to increase the sensitivity of the search, including reference list follow up.

Inclusion and exclusion process of identified citations

The agree search strategy will be applied to the agreed databases and information sources.

A single Reference Manager file will be produced of all references identified through the search process. Duplicates will be removed. Each reference will be given a unique identifier code number.

Two electronic copies of references in this file will be produced, and one set given to each reviewer. Two people will review the papers.

Both reviewers will independently screen each reference title and abstract (if available) from their copies the file, using the agreed inclusion and exclusion criteria. Reviewers will receive an electronic spreadsheet to indicate yes for probable or possible inclusion for each citation, or no for exclusion. At this stage abstracts only will be translated if the citation is not written in English.

The independent screening assessments will be merged.

Where both reviewers have indicated no for a citation then that citation will be excluded at this stage, and the full article will not be obtained.

Where both reviewers have indicated yes for a citation then the full article will be obtained. They will go into the second round of inclusion/exclusion assessment of articles.

Where one reviewer has indicated yes and the other no then the full article will be obtained and go into the second round as above.

The second round will involve each reviewer assessing the full article based on the agreed inclusion/exclusion criteria. Each will decide yes or no for exclusion for each citation reaching the second round.

The second round assessments will be merged.

Where both indicate yes in the second stage the citation will go forward for subsequent data extraction and critical appraisal. Where both indicate no the citations will be excluded. Where there is disagreement then a third reviewer will apply the inclusion/exclusion criteria and their yes or no will be final.

Study data extraction and critical quality appraisal

Data extraction form.

Study characteristics to be collected

1. Relevance or appropriateness of studies gathered for assessing hypothesis to be tested.

2. Rationale for the selection and coding of data.

3. Documentation of how data were classified and coded.

4. Assessment of confounding.

5. Assessment of study quality.

6. Assessment of heterogeneity.

7. Statistical methods.

Results

Descriptive information

Descriptive information for each included study. Details of study design, participants, interventions, definitions of outcomes, will be included in the table of characteristics of included studies. Between study heterogeneity will be assessed and explained. The reasons for excluding any studies will be clearly reported.

Search strategy

Ovid MEDLINE – Search Strategy

Describing ventilation	Number
1. Non invasive ventilation.mp.	
2. exp noninvasive ventilation/	
3. noninvasive ventilation.mp.	
4. CPAP.mp.	
5. exp continuous positive airway pressure/	
6. continuous positive airway pressure.mp.	
7. nasal cannula*.mp.	
8. nasal prong*.mp.	
9. exp oxygen inhalation therapy/	
10. oxygen inhalation therapy.mp.	
11. high-flow.mp.	
12. highflow.mp.	
13. high-flow therapy.mp.	
14. highflow therapy.mp.	
15. humidified high-flow nasal cannula.mp.	
16. HFNC.mp.	
17. high flow nasal cannula.mp.	
18. HHFNC.mp.	
19. heated humidified high-flow nasal cannula.mp.	
20. HHHFNC.mp.	
21. high flow nasal oxygen.mp.	
22. HFNO.mp.	
23. high flow oxygen.mp.	

24. nasal high flow.mp.	
25. optiflow.mp	
26. airvo2.mp	
27. airvo.mp	
28. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	
Describing infant or child	
29. Infant*.mp.	
30. exp Infant/	
31. child*.mp.	
32. exp Child/	
33. 29 or 30 or 31 or 32	
Describing bronchiolitis	
34. exp Bronchiolitis Obliterans/	
35. bronchiolitis.mp.	
36. exp Bronchiolitis/	
37. exp Bronchiolitis, Viral/	
38. bronchopneumonia.mp.	
39. exp Pneumonia, Viral/	
40. exp Bronchopneumonia/	
41. respiratory syncytial virus.mp.	
42. exp Respiratory Syncytial Viruses/	
43. respiratory syncytial viruses.mp.	
44. exp Respiratory Syncytial Virus, Human/	
45. exp Respiratory Syncytial Virus Infections/	
46. RSV.mp.	
47. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or	

42 or 43 or 44 or 45 or 46	
Combining ventilation AND infant or child AND bronchiolitis	
48. 28 AND 33 AND 47	

The following table is an explanation of the symbols used in the search strategy above.

/	after an index term (MeSH heading) indicates that all subheadings were selected.
*	before an index term indicates that that term was focused - i.e. limited to records where the term was a major MeSH/Emtree term.
"exp"	before an index term indicates that the term was exploded.
.tw.	indicates a search for a term in title/abstract
.mp.	indicates a free text search for a term
#	retrieves records that contain the search term with substituted character(s) in the specified location.
*	at the end of a term indicates that this term has been truncated.
*n	The limited truncation symbol, $n, Retrieves records that contain the search term and all possible suffix variations of a root word with the maximum number of characters that may follow the root word or phrase, specified by n.
?	in the middle of a term indicates the use of a wildcard.
adj	indicates a search for two terms where they appear adjacent to one another

Databases and information sources

Bibliographic databases
CINAHL 1982-
Embase 1980-
HMIC Health Management Information Consortium 1979
Medline 1950-
Medline in Process
Scopus
OpenSIGLE
Web of Knowledge Science Citation Index Expanded 1981- Social Science Citation Index 1981- ISI Proceedings 1990-

DATA EXTRACTION FORM AND QUALITY SCORING FORM

STUDY AND COUNT RY	**OBJECTIVE**	**STUDY DESIGN**	**STUDY GROUP**	**CONTROL GROUP**	**OUTCOME MEASURES**	**GUIDELINES/GUIDA NCE ON USE OF HIGHFLOW**	**SUBJECTS (GENDER)**
This is the first author name and country	This is the main objective of the paper	Was it a trial etc.	This includes info on number of children and anything else of interest	This includes info on number of children and anything else of interest	How they measured success or failure etc.	So basically if the paper gives details about how to use the highflow in a ward setting	How many male or female in each group

TYPE OF HIGH FLOW	**AGE**	**YEAR OF BIRTH**	**METHOD OF DEFINING BRONCHIOLI TIS**	**RESULTS**	**QUALITY SCORE**
Brand name etc			ATS or BTS etc.		

Quality	Scores awarded	
Selection		
1) Representativeness of the exposed cohort		
a) truly representative of the average in the community	4	
b) Somewhat representative of the average in the community	3	
c) Selected group of users e.g. nurses, volunteers	2	
d) no description of the derivation of the cohort	1	
2) Selection of the non exposed cohort		
a) Drawn from the same community	3	
b) Drawn from a different source	2	
c) no description of the derivation of the non exposed cohort	1	
3) Ascertainment of exposure (BRONCHIOLITIS)		

a) BTS or ATS	3	
b) Doctor diagnosed no further information	2	
c) no description	1	
4) Demonstration that outcome of interest was not present at start of study		
a) yes	2	
b) no	1	
Outcome		

1) Assessment of outcome		
a) independent blind assessment	4	
b) record linkage	3	
c) self report	2	
d) no description	1	
2) Adequacy of follow up of cohorts		
a) complete follow up all subject accounted for	4	

b) subjects lost to follow up unlikely to introduce bias	3	
c) follow up rate low and no description of those lost	2	
d) no statement	1	

References

1. Abboud P, Roth P, Yacoub N, Stolfi A. Efficacy of high flow/high humidity nasal cannula therapy in viral bronchiolitis. *Critical Care Medicine* 2015;1):177.
2. Bueno Campaña M, Olivares Ortiz J, Notario Muñoz C, Rupérez Lucas M, Fernández Rincón A, Patiño Hernández O, et al. High flow therapy versus hypertonic saline in bronchiolitis: randomised controlled trial. *Archives of Disease in Childhood* 2014;99(6):511-15.
3. Cesar RG, Bispo BRP, Felix P, Modolo MCC, Souza AAF, Horigoshi NK, et al. High-Flow Nasal Cannula versus Continuous Positive Airway Pressure in Critical Bronchiolitis: A Randomized Controlled Pilot. *Journal of Pediatric Intensive Care* 2020;09(04):248-55.
4. Chen DY, Zee ED, Gildengorin G, Fong EW. A pilot study of heated and humidified low flow oxygen therapy: An assessment in infants with mild and moderate bronchiolitis (HHOT AIR study). *Pediatric Pulmonology* 2019;54(5):620-27.
5. Durand P, Guiddir T, Kyheng C, Blanc F, Vignaud O, Epaud R, et al. A randomised trial of high-flow nasal cannula in infants with moderate bronchiolitis. *European Respiratory Journal* 2020;56(1).
6. Ergul AB, Calıskan E, Samsa H, Gokcek I, Kaya A, Zararsiz GE, et al. Using a high-flow nasal cannula provides superior results to OxyMask delivery in moderate to severe bronchiolitis: a randomized controlled study. *European Journal of Pediatrics* 2018;177(8):1299-307.
7. Franklin D, Babl FE, Schlapbach LJ, Oakley E, Craig S, Neutze J, et al. A Randomized Trial of High-Flow Oxygen Therapy in Infants with Bronchiolitis. *New England Journal of Medicine* 2018;378(12):1121-31.
8. Hathorn C, Ernst G, Hasan S, Wong D, Seear M. The hi-FLO study: A prospective open randomised controlled trial of high flow nasal cannula oxygen therapy against standard care in bronchiolitis. *Thorax* 2014;2):A38.
9. Kefala K, Nyamugabo K, Farhat N, Janssen A, Seghaye MC. High-flow nasal cannula heated-humidified (HFNC) oxygen (O2) at 2 litres (lt)/kg/min versus low-flow O2 (up to 2lt/min) in pediatric emergency department (PED) and pediatric ward (PW) in infants with bronchiolitis who need O2 administration: A combined prospective randomized controlled and retrospective study: Preliminary results. *European Respiratory Journal. Conference: European Respiratory Society Annual Congress* 2015;46(SUPPL. 59).
10. Kepreotes E, Whitehead B, Attia J, Oldmeadow C, Collison A, Searles A, et al. High-flow warm humidified oxygen versus standard low-flow nasal cannula oxygen for moderate bronchiolitis (HFWHO RCT): an open, phase 4, randomised controlled trial. *Lancet* 2017;389(10072):930-39.
11. Gonzalez Martinez F, Gonzalez Sanchez MI, Perez-Moreno J, Toledo Del Castillo B, Rodriguez Fernandez R. [What is the optimal flow on starting high-flow oxygen therapy for bronchiolitis treatment in paediatric wards?]. [Spanish]. *Anales de Pediatria. 91(2):112-119, 2019 Aug.* 2019.
12. Mayfield S, Bogossian F, O'Malley L, Schibler A. High-flow nasal cannula oxygen therapy for infants with bronchiolitis: Pilot study. *Journal of Paediatrics and Child Health* 2014;50(5):373-78.
13. Milani GP, Plebani AM, Arturi E, Brusa D, Esposito S, Dell'Era L, et al. Using a high-flow nasal cannula provided superior results to low-flow oxygen delivery in moderate to severe bronchiolitis. *Acta Paediatrica* 2016;105(8):E368-E72.
14. Milési C, Essouri S, Pouyau R, Liet J-M, Afanetti M, Portefaix A, et al. High flow nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) for the initial respiratory management of acute viral bronchiolitis in young infants: a multicenter randomized controlled trial (TRAMONTANE study). *Intensive Care Medicine* 2017;43(2):209-16.

15. Milesi C, Pierre A-F, Deho A, Pouyau R, Liet J-M, Guillot C, et al. A multicenter randomized controlled trial of a 3-L/kg/min versus 2-L/kg/min high-flow nasal cannula flow rate in young infants with severe viral bronchiolitis (TRAMONTANE 2). *Intensive Care Medicine* 2018;44(11):1870-78.
16. Murphy S, Bruckmann E, Doedens LG, Khan AB, Salloo A, Omar S. High-flow oxygen therapy v. standard care in infants with viral bronchiolitis. *Southern African Journal of Critical Care* 2020;36(2):109-13.
17. O'Brien K, Matamoros G, Babbitt C. 1217: DOES A HIGH-FLOW NASAL CANNULA WEANING PROTOCOL FOR BRONCHIOLITIS IMPACT THE DURATION OF THERAPY? *Critical Care Medicine* 2019;47:585-85.
18. Ramnarayan P, Lister P, Dominguez T, Habibi P, Edmonds N, Canter RR, et al. FIRST-line support for Assistance in Breathing in Children (FIRST-ABC): a multicentre pilot randomised controlled trial of high-flow nasal cannula therapy versus continuous positive airway pressure in paediatric critical care. *Critical Care* 2018;22.
19. Sarkar M, Sinha R, Roychowdhoury S, Mukhopadhyay S, Ghosh P, Dutta K, et al. Comparative study between noninvasive continuous positive airway pressure and hot humidified high-flow nasal cannulae as a mode of respiratory support in infants with acute bronchiolitis in pediatric intensive care unit of a Tertiary Care Hospital. *Indian Journal of Critical Care Medicine* 2018;22(2):85-90.
20. Sood R, Stolfi A, Rowin M. Use of high flow high humidity nasal cannula therapy for infants with bronchiolitis. *Journal of Investigative Medicine* 2012;60 (1):453.
21. Ture E, Yazar A, Akn F, Pekcan S. High-flow Nasal Cannula is Superior to Standard Face-Mask Oxygen Therapy in Viral Bronchiolitis. *Signa Vitae* 2020;16(1):47-53.
22. Vahlkvist S, Jurgensen L, la Cour A, Markoew S, Petersen TH, Kofoed PE. High flow nasal cannula and continuous positive airway pressure therapy in treatment of viral bronchiolitis: a randomized clinical trial. *European Journal of Pediatrics* 2020;179(3):513-18.
23. Yurtseven A, Saz EU. The Effectiveness of Heated Humidified High-flow Nasal Cannula in Children with Severe Bacterial Pneumonia in the Emergency Department. *Journal of Pediatric Research* 2020;7(1):71-76.