Supplementary Table 1

Table 1. HFNC treatment failure rates, effects and treatment failure predictors

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| *In Bronchiolitis* | | | | | |
| Study | Patients | HFNC Flow and/or comparator | Failure rate % | Results-Outcome | Predictors, time to first indicator, escalation time |
| Mc Kiernan 2010, one  Retrospective, PICU  Before/after period [80] | 115 patients  <24 months | 57 SOT, *vs.* 58 HFNC, 7–8 L/min, | 23% intubation before *vs.*  9% after HFNC  *p* = 0.043 | 68% less intubation, cost  LOS 4 from 6 days, *p* = 0.0058 | Less RR 60 min *p* < 0.001  Less WOB |
| Abboud 2012, one  Retrospective, PICU  Responders vs NR  [94] | 113 infants  <12 months | HFNC 3–8 L/min  SaO2 >92% | 18.6%  NR less tachypnea and no change in RR after HFNC initiation | Multiple logistic regression: AOR 1.34 per 5 mm increase in capillary PCO2 *p* = 0.007, AOR 0.96 per 1 breath reduction before administration *p* = 0.017  NR higher HFNC flows *p* = 0.006 | Mean time to IMV 14±11 h. NR at 1h: lower pre/post pH *p* < 0.018, higher pre/post PCO2 *p* < 0.001, less pre RR *p* = 0.018, higher PRISM III *p* < 0.001 |
| Bressan 2013, one  Prospective, pilot, PW  Feasibility study  [82] | 27 infants  <12 months | HFNC 7-8 L/min | None escalation of care  Moderate to severe bronchiolitis | No adverse events  Included only Wang score >5 | Increase in SpO2, Decrease 6–8 mmHg in EtCO2, decrease 13–20 in RR *p* < 0.001, from the 1st hour |
| Metge 2014, one  Retrospective, PICU  Before/after period [103] | 34 infants  <12 months | 19 nCPAP  15 HFNC, 1–3 L/kg/min, max 8 L/min  SaO2 >92% | nCPAP 5.26%  HFNC 13.33% | No difference between CPAP before and HFNC after in the management of severe bronchiolitis | ND between groups on HR, RR, FiO2, SpO2, pH, PaCO2, LOS |
| Mayfield 2014, one  Prospective, pilot, ED + PW  [81] | 94 infants  <12 months | 61 HFNC, 2 L/kg/min  Max 10 L/min *vs.* 33 SOT routine  SaO2 >94% | HFNC 13.11%  SOT 30.3% | 4 fold less PICU admission, *p* = 0.043 | Less HR 60 min *p* = 0.02  Less RR 180 min *p* < 0.05 |
| Milesi 2017, multi  TRAMONTANE  Prospective, RCT  PICU  [106] | 142 infants  <6 months | 71 HFNC, 2 L/kg/min *vs.* 71 nCPAP  7 cmH2O  SaO2 94% –97% | HFNC 50.7%  nCPAP 31%  Standard failure criteria | nCPAP better  RR success 1.63 *p* = 0.001  nCPAP failures higher weight *p* = 0.04  HFNC failures higher baseline FiO2 *p* = 0.02  ND in intubation rate, duration of IMV, LOS | 60% of failures within 6 h  ND in mean failure time 6.7 h in HFNC *vs.* 9.7 h in nCPAP *p* = 0.19 |
| Kepreotes 2017, one  Prospective, RCT  ED + PW  [32] | 202 patients  <24 months | 101 HFNC, 1 ml/kg/min  *vs.* 101 SOT, 2L/min  SaO2 >94% | HFNC 14%  SOT 33%  63% of patients failed in SOT rescued by HFNC | Less PICU admission, cost  HFNC better comfort *p* = 0.017, feeding *p* = 0.01 | HFNC longer time to failure 0.9 days *vs.* 0.6 days (24h) *p* < 0.0001, ND in LOT, intubation, PICU, LOS |
| Heikkila 2018, multi  Retrospective,  PW + PICU  [88]  Responders *vs*. NR | 88 infants  <12 months | 53 PW  35 PICU  HFNC 5–6 L/min | 0 PW  34% PICU  14% overall | Failure predictors: prematurity *p* = 0.006, low gestational age *p* = 0.002, low birthweight *p* = 0.001  Shorter HS 6 vs 8 days in responders, *p* = 0.014 | Less HR 60 min *p* = 0.008  Better SpO2 60 min *p* = 0.000  Less RR 360 min *p* = 0.002 |
| Sarkar 2018, one  Prospective, RCT PICU  [70] | 31 infants  28 days–12 months  RDAI >11 | 15 HFNC, 2L/kg/min up 10kg + 0.5 L/kg after  16 nCPAP 4–8 cmH2O | HFNC 6.66%  CPAP 6.25%  *p* = 0.29 | HFNC equally effective to nCPAP, better tolerance; better HR *p* < 0.001, better comfort score *p* < 0.001, less nasal injury *p* = 0.021  ND in IMV rate, NIV duration and LOS | ND in SpO2, RR, PaO2, PCO2, and RDAI scores  between the two groups, all improved steadily |
| Franklin 2018, multi  PARIS  Prospective, RCT  ED + PW  [34] | 1472 infants  <12 months | 739 HFNC,  0–12kg 2 L /kg/min max 25 L/min *vs.* 733 SOT, 2 L/min, nasal cannula  SaO2  92%–94% | 12% in HFNC  *Vs.* 23% in SOT  *p* < 0.001  61% failed in SOT rescued by HFNC  Standard escalation criteria or clinical | Escalation if ¾ criteria  Stable or increased HR  Stable or increased RR  Increase in FiO2 >40% or >2L/min  Early hospital warning tool  ND in LOT, LOS, HS | ND in escalation criteria and escalation time (~ 0.7 days), HR, SaO2  RR highest at escalation *p* < 0.001 |
| Guillot 2018, one  Prospective observational, PICU  Before routine care/after HFNC as first line treatment, Responders vs NR in the after period  [95] | 102 infants  <12 months | 41 before *vs.* 61 after  2 L/kg/min HFNC *vs.* nCPAP 4–6 cmH2O/BIPAP/IMV | In after period only HFNC 38.5%  Before use: HFNC 34%,  cCPAP/BIPAP 56%, IMV 10%  After use: HFNC 90%,  cCPAP/BIPAP 5%, IMV 5% | HFNC use increased in after period 90% *vs.* 34%, *p* < 0.0001  No difference in intubation rates at admission, during CPAP/BIPAP period or overall LOS | HFNC failure: bivariate HR, pH and PaCO2 in COX model  Independent Hazard Risk 1.37 per 5 mmHg increase in PaCO2  61.9% of HFNC failures within 12 h, 76.2% within 24 h |
| Habra 2020, one  Retrospective, PICU  [105] | 137 patients  1month–2 years | 77 HFNC *vs.* 10 CPAP *vs*. 50 BIPAP | HFNC 50.6%  CPAP 0%  BIPAP 8% | HFNC higher failure *p* < 0.01, 90% rescued by BIPAP | ND in LOS, HS |
| Cesar 2020, one  Prospective, RCT, PICU  [104] | 61 patients < 9 months | 35 HFNC, 1.5 L/Kg/min  28 CPAP 6 cmH2O  SaO2 >93% | HFNC 37.1%  CPAP 35.7%  ND, *p* = 0.88 | HFNC TF similar to CPAP  Critical bronchiolitis with  mWood-Downes score >4  ND in LOS *p* = 0.46 | Median TF time  15.2 h in HFNC 18.5 h in CPAP |
| Vahlkvist 2020, two  Prospective, RCT,  PW  [71] | 50 patients  <2 years | 22 HFNC 2 L/Kg/min *vs.* 28 CPAP 12–14 L/min | HFNC 9.09%  CPAP 7.14% | ND in treatment failure, PICU transfer, HS between groups  HFNC pleasant and effective alternative to CPAP | ND mean RR, FiO2, or pCO2 during 48 h  ND in mWCAS  HFNC lower NIPS (*p* < 0.05) |
| Fabre 2021, multi  Retrospective, PW  Real life study  [74] | 138 infants  <3 months | HFNC *vs.* SOT or supportive therapy only | PICU transfer rate: HFNC 2.9%, SOT 44%, other 16.3% *p* = 0.033 | Wang clinical score  EDIN comfort score  Transfer to PICU  Less cost | HFNC pts 0–24 h: less Wang *p* = 0.002, less EDIN *p* < 0.0001,  Less PICU *p* = 0.033 |
| *All causes of Respiratory Failure* | | | | | |
| Schibler 2011, one  Retrospective, PICU  Before/period  [86] | 298 patients  <24 months  AHRF  56% Bronc. | HFNC 4-8 L/min  SaO2 >94% | Overall 30.87%  19% NIV  12% IMV  Bronch. 4% IMV  Cardiac 50% IMV | Decrease intubation in bronchiolitis from 37% to 7%. Patients with escalation to NIV higher PIM, FiO2, LOS, *p* < 0.01 | Responders 20% less HR and RR in 90 min *p* < 0.05 |
| Kelly 2013, 2 centers  Retrospective, ED  [96] | 498 patients  <2 years  AHRF  46% Bronc. |  | 8%  Intubation rate | Bronchiolitis protective for HFNC failure OR 0.4 | Initials: RR >90th OR 2.11, venous PCO2 >50 mmHg OR 2.51, venous pH <7.3 OR 2.53 |
| Testa, 2014, one  RCT, Cardiac PICU  [93] | <18 months  PERF only | 46 SOT 2 L/min *vs*. 43 HFNC 2 L/kg/min | SOT 15% *vs.*  HFNC 0%, *p* = 0.008 | PaCO2 similar within groups in entire study period (*p* = 0.5), ND in ventilation time (*p* = 0.78), intubation rate (*p* = 1) and LOS (*p* = 0.5) | Bivariate HFNC better PaO2 at 1, 6, 12, 24, 48 h and better PaO2/FiO2 at 1, 6, 12, 24, 48 h (*p* < 0.05)  TFP PaO2/FiO2 at 6 h (*p* = 0.006) and at 24 h (p = 0.002) |
| Wraight 2015, one  Rerospective  Responders vs NR [83] | 54 patients  AHRF  79% Bronc. |  | 22%  7 rescued to CPAP  5 IMV | Median age 3.5 months (1-10)  Cardiac patients 50% failure  HFNV failures longer LOS *p* = 0.04 | Median HFNC failure time 5.5 h, 75% within 8.25 h  RR higher in failures at 1h *p* = 0.037 |
| Betters 2017, one  Retrospective, PW  [92] | 231 patients | HFNC | 6% | TF was greater in cardiac history (*p* = 0.026), intubation history (*p* = 0.04), and in higher FiO2 needs *p* < 0.001) | TFP: Higher in higher FiO2 needs (OR 38.3, *p* = 0.002), and less likely in Bronchiolitis (OR 0.3), *p* = 0.048). |
| Shioji 2017, one  Prospective, observational  Cardiac PICU  Responders vs NR [84] | 20 patients  <48 months  PERF only | HFNC 2 L/kg/min | 5% | Median age 4.5 months (2.3-14)  Median BW 4.3 kg (3.1-7.1) | Less RR 1 h *p* = 0.0008  Less Systolic blood pressure 1 h *p* = 0.003  Stable PaCO2 *p* = 0.05 |
| Kamit 2018, one  Prospective, PICU  Responders vs NR [90] | 204 patients  1 month to 18 years  AHRF and PERF |  | 12.7%  4 NIV  22 IMV | Median age 16.5 months | TFP: Age >120 months, Higher PRISM III,  Lower SpO2/FiO2 < 200 at 60 min |
| Er 2018, one  Retrospective, ED  Responders vs NR [85] | 154 patients  AHRF  38.3% Bron.  61.7% Pneumonia |  | 16.2% | Median age 10 months (5.7-22.5)  NR lower initial PaO2 and S/F *p* = 0.002, lower venous pH *p* = 0.012, higher PaCO2 *p* = 0.001  Cut-off S/F 195 at 1 h | Median time to escalation 7 h (4–20)  Responders at 1h: Better Rr, mRDAI, S/F ratio |
| Ramnarayan 2018, multi, pilot RCT, PICU, FIRST-ABC  Feasibility study  [68] | 113 pts  1 month to 16 years  AHRF and PERF | 59 HFNC weight banded flows *vs.* 54 CPAP 6-8 cmH2O | Intubation at 72 h, ND  HFNC 25.4%  CPAP 18.5%, *p* = 0.38 | Mean mCOMFORT scores at 6 h, higher in CPAP intolerance (19 ± 4.4) *vs*. HFNC (15.3 ± 3.1)  HFNC less ventilator-free days at day 28 | Median time to IMV HFNC 5.5 h (1.7–17.3) *vs*. CPAP 3.3 (1.6–19.8) |
| Hansen 2019, one  Retrospective, PW  Responders vs NR [109] | 18 patients  <17 years  AHRF |  | 56%  80% rescued by CPAP/BIPAP | Clinical respiratory PEWS  None intubated  ND in air leakage or days of respiratory support | NR in 90min: higher initial *p* = 0.03 and worsening *p* = 0.05 PEWS scores |
| Liu Cong, 2020, one  Prospective RCT, PW  [69] | 84 patients  <2 years  Pneumonia | 43 2 L/kg/min, max 20 L/min *vs.* 41 CPAP 4-6 cmH2O  SaO2 92%–94% | HFNC 14%  CPAP 10%, *p* > 0.05 | HFNC alternative to CPAP  HFNC better tolerance and less adverse events *p* = 0.005, less sedatives *p* = 0.000, less gastric distention *p* = 0.066, less skin lesions *p* = 0.036  Shorter LOS *p* = 0.042 days | Higher HR in HFNC TF *vs.* CPAP *p* = 0.005. ND in RR, PaO2, PaO2/FiO2, SpO2, PaCO2 and pH in 1, 24 and 48 h  ND in HS, support time, mortality |
| Richards 2020, one  Retrospective, PW  Before/after period [110] | 90 pts  2 months to 13 years  AHRF | HFNC | 6.66% | Less patients tertiary transfer *p* < 0.05, IMV *p* < 0.01, died *p* = 0.02 | Median time HFNC failure 11 h *vs*. 60 h for success |
| Franklin 2021, multi  Prospective, RCT  ED + PW  [25] | 563 pts  1 month to 16 years  AHRF  47% Restrictive  17% Pneum.  8% Bronch. | 280 SOT  283 HFNC at 0–12 kg 2 L/kg/min, max 25  13- 15 kg 30 L/min  16- 30 kg 35 L/min  31- 50 kg 40 L/min  >50 kg 50 L/min  SaO2 >92% | 11.7% in HFNC vs 18.1% in SOT, OR 0.62  60% failed in SOT rescued by HFNC  Standard escalation criteria or clinical | Obstructive HFNC failure 9.7% *vs*. 17.4% in SOT  Risk difference -7.7% in obstructive AHRF  ND in non-obstructive (not wheezing) AHRF  ND in LOT, LOS, HS | Median (IQR) time 0.14 (0.056-0.52d), ¾ escalation criteria OR 1.36, Tachypnea OR 2.11, Tachycardia OR 1.99, Increased O2 OR 1,22, Clinical OR 1.25 |
| Ongun 2021, multi  Prospective, RCT, PICU  [73] | 352 patients  1 month to 18 years  AHRF and PERF | HFNC *vs.* NIPPV  Mostly CPAP/BIPAP | HFNC 11%  NIPPV 17.6%  NIV failures overall higher complication rates (*p* < 0.001) | NIIPV older (*p* = 0.002), longer intubation period (*p* < 0.001), ARDS and LTI (*p* < 0.001). Failure causes: respiratory 63.9%, hemodynamic 17% bulbar dysfunction 10.6%, neurologic 8.5% | NIV failures overall:  RR reduction <10% in 60 min  PRISM III >8  FiO2 >55% at 6 h |
| Lu 2021, one Prospective, PICU  [89] | 153 patients  1 year–14 years  74 AHRF  79 PERF | 2 L/kg/min max 60 L/min  Target SaO2  94%–97% | 0 PERF  29.8% first line  14.4% overall | PaO2/FiO2 ROC 0.99  Optimal cut-off value for PaO2/FiO2 in predicting HFNC success 232 mmHg | Better PaO2 1, 6, + 48 h, *p* < 0.01  Better SpO2 1, 6, + 48 h, *p* < 0.01  PaO2/FiO2 1, 6, 12, 24, 48 + 48 h *p* < 0.01 |
| Asseri 2021, one  Retrospective, PICU  Responders *vs*. NR [97] | 92 patients  1 month–12 years  70 AHRF  22 PERF | 2 L/kg/min, max 30 L | 23% | Higher failure rate among children with chronic diseases (*p* = 0.038) and air-leak syndrome (*p* < 0.001) | NR: Higher HR 48 h *p* = 0.018, higher RR 48 h *p* < 0.001, lower diastolic blood pressure 48 h *p* = 0.011, higher HCO3- 8, 48 h *p* < 0.05, higher PaCO2 8, 48 h *p* < 0.001 |
| Chang 2021, one  Retrospective, PICU  Responders vs NR [91] | 102 patients  1month – 18 years  AHRF No PERF | HFNC at  0-15 kg 2 L/kg/min  16-30 kg 35 L/min  31-50 kg 40 L/min  >50 kg 50 L/min | 15.7%  2 NIV  11 IMV | Mean age 7.00 ± 6.79 years  ROCs of initial and lowest S/F ratio for HFNC failure were 0.786 and 0.816, respectively, and both cut-off S/F ratio values 212 | Mean failure time 24.38 ± 30.96 h. TFP:  FiO2 initial (*p* = 0.002) and max (*p* < 0.001)  S/F initial and lowest (*p* < 0.001) |
| Yildizas 2021, one  Prospective observational  ED+PW+PICU  [99] | 131 patients  1 month–18 years  AHRF Pneumonia 57.3% | 1 L/kg/min and FiO2 0.6  Up to 2.5 L/kg/min  SaO2 >92% | 11.5%  13 IMV  2 NIV | Median age 23 (9-92) months  ROC p-ROXI 24 h 0.79  ROC p-ROXV 24 h 0.72  ROC p-ROXI 48 h 0.88  ROC p-ROXV 48 h 0.88 | Time to failure 0.8 day. Cut-off p-ROXI <65 and p-ROXV <24 at 24 h failure 40%, at 48 h failure 100% |
| Saeed 2021, one Retrospective, PICU Responders *vs*. NR [30] | 120 patients  AHRF | 2 L/kg/min | 23.33% | Barotrauma high 3.3% Mortality high in NR 47.36% vs 10.46%, *p* = 0.001 | Responders: Less HR at 2h *p* = 0.034, end *p* = 0.01, RR less end *p* = 0.003 |
| *Severe Asthmatic Exacerbations* | | | | | |
| Pilar 2017, one  Retrospective, PICU  [108] | 42 pts | 22 HFNC *vs.* 20 NIV | HFNC 40%, escalation to NIV  NIV 0% | HFNC failures respiratory support and LOS longer | Caution not to delay NIV |
| Ballestero 2018, one  Prospective, RCT, ED [116] | 62 pts  1–14 years | 30 HFNC *vs.* 32 SOT | 16/32 (53%) improvement ≥2 PS *vs.* 9/32 (28%), *p* = 0.01 | Moderate to severe asthma with Pulmonary score PS ≥6 and SpO2 <94% | HFNC superior to SOT at 2 h with improvement in PS ≥2 |
| Gonzalez 2019, one  Retrospective, PW  [87] | 536 pts  4–15 years  Acute Asthma only  40 HFNC | HFNC *vs.* SOT and HFNC 15 L/min *vs.* HFNC <15 L/min |  | Median age 5 (4–6) years  Pulmonary score PS  Less PICU admission for HFNC >15 L/min, 13% *vs.* 47%, *p* = 0.05 | HFNC at 3–6 h: Less HR, RR and PS |
| Russi 2021, one  Retrospective [107] | 39 pts  5–17 years | 13 HFNC *vs.* 26 BIPAP |  | BIPAP older *p* < 0.01, greater severity *p* < 0.01, prior PICU *p* = 0.01, more sedation *p* = 0.02, more continuous albuterol *p* = 0.03. HFNC more com. pneumonia *p* < 0.01 | ND in NIV duration, IMV, LOS, mortality |
| *HFNC META-ANALYSES* | | | | | |
| Lin 2019, in Bronchiolitis [100] | 9 RCT  2121 patients | HFNC *vs.* SOT *vs.* CPAP | HFNC treatment failure reduced Risk Ratio 0.5, *p* < 0.01, compared to SOT but increased  Risk Ratio 1.61, *p* = 0.02, compared to CPAP  HFNC HS reduced to SOT in low and middle-income countries | | ND among groups in LOT, HS, PICU admission, IMV, RR, SpO2, adverse events |
| Luo 2019, in all causes of AHRF [101] | < 5 years  8 RCT  2259 pat.  SOT 980 HFNC 1100  CPAP 179 | HFNC *vs.* SOT *vs.* nCPAP | HFNC treatment failure reduced Risk Ratio 0.49, *p* < 0.001, compared to SOT but increased  Risk Ratio 1.74, *p* = 0.004, compared to nCPAP  HFNC lower nasal trauma to nCPAP Risk Ratio 0.35 *p* = 0.009 | | ND among groups in IMV and mortality |
| Catano-Jaramillo 2020, in Bronchiolitis [72] | 3 RCT  HFNC 121  CPAP 115 | HFNC *vs.* CPAP | CPAP treatment failure reduced Risk Ratio 0.7, *p* = 0.05, and longer time MD 3.16, *p* = 0.0001 to failure. More skin lesions Risk Ratio 2.47, *p* = 0.02 in CPAP | | ND in IMV, apnea LOS, HS |
| Dafydd 2021, in Bronchiolitis  [102] | <24 months  15 RCT | HFNC *vs.* SOT *vs.* CPAP | 5 RCT, 1039 patients HFNC superior to 1011 patients SOT, OR 0.44, *p* < 0.0001  4 RCT, 142 patients HFNC ND to 143 patients CPAP, OR 1.64, *p* = 0.07  4 RCT 1041 patients HFNC ND adverse events to 1047 patients SOT, OR 1.47, *p* = 0.45 | | HFNC safe to use in acute hospital settings |

Abbreviations: *PICU*, Pediatric Intensive Care Unit; *SOT*, Standard Oxygen Therapy; *HFNC*, High Flow Nasal Cannula; *LOS*, Length of PICU Stay; *RR*, Respiratory rate; *WOB*, Work of Breathing; *NR*, Non-Responders; *SpO2*; Saturation oxygen peripheral, *AOR*; Adjust Odds Ratio, *IMV*; Invasive Mechanical Ventilation, *PRISM III*; Pediatric Risk of Mortality III, *PW*; Pediatric Ward, *nCPAP*; nasal Continuous Positive Airway Pressure, *ND*; no Difference, *HR*; Heart rate, *FiO2*; Fraction inspired Oxygen, *ED*; Emergency Department, *RCT*; Randomized Control Trial, *LOT*; Length of Oxygen Therapy, *HS*; Hospital Stay, *RDAI*; Respiratory Distress Assessment Index, *BIPAP*; Bilevel Positive Airway Pressure, *mWCAS*; modified Wood Clinical Asthma Score, *NIPS*; Neonatal Infant Pain Score, *AHRF*; Acute Hypoxemic Respiratory Failure, *NIV*; Non Invasive Ventilation, *PIM*; Pediatric Index of Mortality, *TF*; Treatment failure, *TFP*; Treatment failure predictors, *PERF*; Post Extubation Respiratory Failure, *S/F*; S*p*O2/FiO2 ratio, *PEWS*; Pediatric Early Warning Score, *OR*; Odds Ratio, *NIPPV*; non Invasive Positive Pressure Ventilation, *ROC*: Receiver Operational Characteristic, *ROX*; Respiratory-rate Oxygenation index