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**CADTH RAPID RESPONSE REPORT:**
**SUMMARY WITH CRITICAL APPRAISAL**

# Heated Humidified High Flow Oxygen for Respiratory Support: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines


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## Abbreviations

| | |
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| NHF | Nasal high flow therapy |
| COT | Conventional oxygen therapy |
| NIV | Non-invasive ventilation |
| ICU | Intensive care unit |
| RCT | Randomized controlled trial |
| 95% CI | 95% confidence interval |
| RR | Risk Ratio |
| HR | Hazard Ratio |
| OR | Odds Ratio |
| CPAP | Continuous Positive Airway Pressure |
| IMV | Invasive Mechanical Ventilation |
| PaCO2 | Partial Pressure of Carbon Dioxide |
| PaO2 | Partial Pressure of Oxygen |
| FiO2 | Fraction of Inspired Oxygen |
| SpO2 | Pulse Oximetry |
| PtCO2 | Transcutaneous carbon dioxide tension |
| ARF | Acute Respiratory Failure |
| COPD | Chronic obstructive pulmonary disease |

## Context and Policy Issues

Oxygen and/or respiratory support are required for patients in emergency rooms, on the ward and/or in critical care settings during respiratory failure. The most common method to treat this issue, non-invasive ventilation (NIV), is a form of mechanical ventilation that does not require a more invasive endotracheal tube. Most commonly, it inflates the lungs by applying positive pressure to the airway.[1] This can be used in conjunction with or instead of conventional oxygen therapy (COT), including a simple face mask which delivers oxygen.[2]

Though commonly used for acute respiratory failure, NIV and COT have limitations. NIV can deliver the same physiologic effects of invasive mechanical ventilation thus preventing the associated risks of intubation including airway trauma, infections and the need for sedation.[3] However, it can be poorly tolerated due to a tight-fitting interface (most commonly oronasal) which is uncomfortable, prone to leakage, and can result in nasal trauma. Further, the benefit over COT has been questioned.[4] COT does not provide a reliable fraction of inspired oxygen ($FiO_2$) or respiratory support, which could increase the need for escalation to more invasive ventilation.[5] Inadequate warming and humidification also make it intolerable for long periods.[3] Dry air can result in dry nose, throat and nasal pain, and reduced mucociliary clearance.[6] Finally, the flow rate of standard oxygen delivery is usually lower (<15 L/min) than the high inspiratory flow rate of patients in respiratory distress (often 30 to > 120 L/min).[6]

Heated, humidified, high flow oxygen is promising because it addresses some of the limitations associated with other oxygen therapies. Oxygen is heated and humidified, and then delivered to the patient usually through nasal cannulae in nasal high flow (NHF) therapy. Up to 100% humidified oxygen can be delivered at a high flow rate (up to 60 L/min) that meets inspiration flow rates, minimizing room air entrainment. The provider sets the flow rate and $Fi0_2$.[3] NHF is most commonly used oxygenating patients with severe acute respiratory failure from medical conditions such as pneumonia or bronchiolitis in children.[3] Compared to NIV, NHF decreases anatomical dead space and thus improves alveolar

ventilation, though it cannot actively increase inspiratory tidal volume as in NIV. It is also associated with less nasal trauma.[6]

Though it is promising and increasingly being used,[6] there are currently no set recommendations for practical application. It is unclear whether greater patient tolerance translates into clinical benefit. [3]

## Research Questions

1. What is the clinical effectiveness of heated humidified high flow oxygen in hospital and during transfers?
2. What is the cost-effectiveness of heated humidified high flow oxygen compared with other respiratory support?
3. What are the evidence-based guidelines for use of heated humidified high flow oxygen in hospital and during patient transfers?

## Key Findings

There are a substantial number of studies assessing heated, humidified high flow oxygen.

The evidence suggests that heated, humidified high flow oxygen. may help to avert the need for intubation relative to conventional oxygen therapy or non-invasive ventilation, though the findings were not consistent.

The evidence does not suggest that the length of hospitals stays or oxygenation outcomes are better with high flow oxygen relative to conventional oxygen therapy or non-invasive ventilation. Patient comfort outcomes were not systematically studied, but may be improved with heated high flow oxygen. No included study assessed the intervention during hospital transfers, and studies of non-neonatal pediatric patients were limited in both quality and quantity.

Heated, humidified high flow oxygen may be both less costly and more effective to avert intubations, however this was based on one UK-based cost-effectiveness analysis.

No relevant evidence-based guidelines on the use of heated, humidified high flow oxygen were identified. The systematic reviews retrieved in this review generally had a low risk of bias, however the clinical trials were more mixed. The main risks of bias in the clinical trials stemmed from small sample sizes, unclear primary outcomes, and lack of blinding.

## Methods

### Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and January 16, 2019.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

## Table 1: Selection Criteria

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| **Population** | Pediatric (non-neonatal, non-premature) or adult patients being treated in hospital with an airway exacerbation or hypoxemic respiratory failure needing respiratory support |
| **Intervention** | Heated humidified high flow oxygen |
| **Comparator** | Any active comparator |
| **Outcomes** | Q1: Clinical benefit and harms<br>Q2: Cost-effectiveness<br>Q3: Guidelines |
| **Study Designs** | Health technology assessments, systematic reviews, randomized controlled trials, cost-effectiveness studies, and guidelines |

### Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Primary studies where the intervention was to prevent respiratory failure, for example in peri-operative or post-extubation settings, were excluded. Studies with mixed pediatric populations were excluded when results were not analyzed and presented separately for the population of interest to this report (i.e., non-neonatal and non-premature patients). Systematic reviews with a complete overlap of articles with another included systematic review, primary studies that were found in included systematic reviews, and guidelines with unclear methodology were also excluded.

### Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using AMSTAR,[7] randomized studies were critically appraised using Downs and Black,[8] economic studies were assessed using the Drummond checklist.[9] No guidelines were identified. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

## Summary of Evidence

### Quantity of Research Available

536 citations were retrieved from the literature search and 19 potentially relevant reports were retrieved from other sources. Of these, 72 full-text reports were reviewed and 55 were excluded. Eight systematic reviews, eight randomized controlled trials, and one cost-effectiveness study were ultimately included. No relevant guidelines were identified. Appendix 1 presents the PRISMA[10] flowchart of the study selection.

## Summary of Study Characteristics

A full description of study characteristics is available in Appendix 2.

### *Study Design*

Of the eight systematic reviews, three considered RCTs as the only design eligible for inclusion,[11-14] while four systematic reviews included RCTs and observational studies.[4,15,16] The remaining systematic review was restricted to experimental and quasi-experimental studies.[17]

The systematic reviews included literature up to years ranging from 2013 to 2018. Sklar *et al*[4] included literature from database inception up to 2018, and reported on four RCTs and nine observational cohort studies.[4] Three systematic reviews included literature from database inception to 2016.[11,14,16] Of these, one included four RCTs,[14] one included six RCTs,[11] and the third one included 12 RCTs[16] and two prospective cohort studies. Nedel *et al*[12] included literature from database inception to 2015[12] and identified nine RCTs, and Mayfield *et al*[17] did not identify any relevant studies, concluding its search in 2013.[17] Two systematic reviews did not specify search dates.[13,15] There was substantial overlap between all the systematic reviews, as highlighted in Appendix 5.

Among the eight clinical trials, two were single-centre randomized crossover studies where each subject received both treatment and control therapies in a randomized order.[18,19] Of the remaining trials, two were multi-centre, parallel group studies, stratified by study site.[2,20] Of these, one was a pilot study,[20] and four were single-centre RCTs.[21-24]

One study conducted a cost-effectiveness analysis. It used a decision analytic model in Microsoft Excel® based on 100 patients. A five-year life time for the oxygen therapy device was assumed, and the scenario was its use as first-line therapy for acute respiratory failure (ARF). The model parameters were informed by three RCTs, and the cost perspective was from the UK's National Health Service. The study conducted deterministic and probabilistic sensitivity analysis.[25]

### *Country of Origin*

The eight systematic reviews did not have geographic restrictions for study inclusion, but first authors were based in Canada,[4] China,[11,14,16] Brazil,[12] the UK,[13] the U.S.[15] and Australia.[17]

The RCTs included in this review were conducted in Thailand,[21,24] Turkey,[23] the UK,[20] Spain,[22] and France,[2] while the randomized cross-over studies were in New Zealand[18] and Italy.[19] The cost-effectiveness study was conducted in the UK.[25]

### *Patient Population*

**Systematic reviews**

All the systematic reviews and randomized studies were limited to hospital settings. Seven systematic reviews were limited to adults,[4,11-16] with two further specifying these as aged 18 and older[16] or 16 and older.[11] Mayfield *et al*[17] included children aged four weeks to 16 years old. All studies included patients requiring respiratory support, though one excluded a diagnosis of bronchiolitis as the underlying cause.[17] One systematic review included patients who were immunosuppressed only, and in this review infectious pneumonia was the primary cause of ARF.[4] The causes of ARF in other systematic reviews were variable

including, for example, complications related to cardiac surgeries.[13,15] The total patient numbers included in the systematic reviews were 2,078, [15] 2,507,[13] 3,881,[16] 1,892,[11] 1,956[4] and 703.[14] One study did not report the total,[12] and another did not retrieve any studies.[17]

**Randomized studies**

Four randomized studies examined the use of respiratory support in pediatric patients. These included 60 children aged one to 24 months,[23] 98 children aged one month to five years old,[24] 60 children aged one year to 14 years,[22] and 29 children aged 6 weeks to 16 years.[20] The remaining studies were in adult populations. Two studies included adults aged 18 years and older,[2,21] with 776[2] and 128[21] participants, and one study included 24 adults aged 16 years and older.[18] One study did not specify the age but included 15 adults.[19] Finally, one trial was limited to patients who were immunosuppressed.[2]

All studies included patients requiring respiratory support which was defined in different ways. Three studies specified a list of optional criteria, at least one of which had to be met, i.e. patients experiencing one of oxygen saturation < 92% in $FiO_2$ > 0.40, respiratory acidosis (pH < 7.3) or moderate respiratory distress,[20] one of partial pressure of oxygen ($PaO_2$) < 60 mm Hg**,** pulse oximetry ($SpO_2$) < 90%, tachypnea > 30/minute, or respiratory distress,[2] one of a pulmonary score >=6 or $SpO_2$ < 94%,[22] and one of a high respiratory rate, signs of increased work of breathing or oxygen saturation below 95%.[24] One study specified respiratory distress as an $SpO_2$ <95%, and a respiratory rate greater than 24 breaths/minute,[21] while the remaining study required a moderate to severe bronchiolitis diagnosis.[23] This was defined as evidence of a viral respiratory tract infection and $SpO_2$ < 92% as specified by National Institute for Clinical Excellence guidelines.[23] The remaining two studies did not restrict the inclusion of participants beyond the requirement to have new or acutely worsening respiratory symptoms[19] or respiratory symptoms related to a chronic obstructive pulmonary disease (COPD) exacerbation.[18]

Infectious pneumonia was the primary cause of ARF in the study that only included patients who were immunosuppressed,[2] and in one pediatric study,[24] while lung disease was the primary cause in another pediatric study.[20] Three studies were limited to specific causes of ARF including moderate to severe bronchiolitis,[23] asthma exacerbations,[22] and acute COPD exacerbations.[18]

The most common exclusion criteria were subjects that presented with an indication for immediate and/or more advanced respiratory support.[2,19-24] One study did not specify exclusion criteria but did ultimately exclude patients with clinical instability.[18] Three studies excluded patients with facial or cranial abnormalities such as a deviated septum that precluded using the oxygen interfaces required in the intervention and control groups.[19,20,23] Two studies excluded patients with heart conditions including cardiovascular disease[23] or congenital cyanotic heart disease,[24] while two excluded those with lung conditions including chronic lung disease,[23] COPD,[19] and concomitant pneumonia.[21] Finally, two studies excluded patients with cardiogenic pulmonary edema.[2,19]

**Cost-effectiveness study**

The cost-effectiveness study was based on intensive care unit (ICU) patients with ARF who had not undergone endotracheal intubation.[25]

*Interventions and Comparators*

**Systematic reviews**

Seven systematic reviews compared NHF to NIV, COT, or combined NIV and COT. The interventions and comparators were further specified in four reviews. For the intervention, NHF was defined as flow rates greater than 2L/min,[17] and 15 L/min.[11] The comparator was further defined as COT through nasal prongs, face or Venturi masks in one study,[14] and in another, the comparators were COT through nasal cannula or masks and NIV using a face mask connected to an ICU ventilator. Ni *et al.* specified the type of NIV as positive pressure ventilation,[16] while Mayfield specified the comparator as continuous positive airway pressure (CPAP) or bi-level positive airway pressure through facial or nasal mask or nasal cannula.[17]

**Randomized studies**

The interventions were all heated, humidified NHF therapy. In adult studies, NHF was initiated at 50 L/min,[2] 35 L/min,[18,21] and 40 L/min[19]. The flow rate was increased to a maximum of 60 L/min in two studies depending on clinical need to achieve an $SpO_2$ ≥ 95%.[2,21] $FiO_2$ was initiated at 100% in one study and tapered when $SpO_2$ reached 95%.[2] In two studies, $FiO_2$ was clinically determined based on the patients' status.[19,21] One adult study did not specify the method to determine initial $FiO_2$.[18] In pediatric studies, the flow rate of NHF depended on child age and weight, and two studies specified that $FiO_2$ depended on demand to achieve 94%[23] or 95%[24] oxygen saturation. One study varied the flow rate over time with an approximate average of 1.5 L/kg/min.[20] The flow rate was delivered at a maximum of 60 L/min in a study including older children or adolescents,[22] 20 L/min in a study of children up to 24 months,[23] and 30 L/min where children up to 5 years were included.[24]

The comparators in the randomized studies included CPAP delivered through a helmet, nasal prong or mask,[20] COT delivered using any device,[2,22] COT delivered through a nasal cannula,[21,24] nonrebreather mask,[21] or an Oxymask.[23] In the randomized crossover studies, the comparators were a standard non-occlusive face mask with 12 L/min gas flow[19] and COT delivered via nasal prongs [18] administered to the same patients after NHF. The intervention and comparator treatments in these studies were delivered for 20[19] and 30 minutes each.[18] One of these crossover studies specified a 15 minute washout period between the two treatments,[18] while the other did not specify a washout period.[19]

**Cost studies**

The intervention in the cost study was Optiflow nasal high flow and the comparator was COT using a nonrebreather face mask, or NIV using a face mask and ICU ventilator.[25]

*Outcomes*

**Systematic reviews**

All systematic reviews considered the rate of invasive mechanical ventilation (IMV), endotracheal intubation and/or escalation of respiratory support as their primary,[11,12,14,17] secondary[4,13] or unspecified[15,16] outcome. Hospital mortality was also considered as a primary,[4,13,17] secondary[11,12,14] or unspecified[15,16] outcome in all studies. Three studies considered oxygenation outcomes, such as $PaO_2$:$FiO_2$ ratio[11,12] or oxygen saturation[15] and four studies considered length of stay in the ICU as secondary or unspecified outcomes.[11,15-17]

**Randomized studies**

Mortality at 28 days,[2] transcutaneous carbon dioxide tension ($PtCO_2$) at 30 minutes,[18] respiratory rate at 60 minutes,[21] change in asthma severity (decrease in pulmonary score by ≥ 2 at 2 hours)[22] and treatment failure (two of no change in respiratory rate, heart rate and persistence of $SpO_2$ < 92%)[23] were the specified primary outcomes. Three studies did not specify a primary outcome, but the outcomes ultimately included ICU and hospital length of stay,[20] intubation rate,[20] and failure rate. The latter was defined as two of not returning to a respiratory rate within 20% of normal, not returning to a heart rate to within 20% of normal and $FiO_2$ < 0.5.[24] The third study collected a variety of outcomes related to breathing, ventilation, gas exchange, and hemodynamics.[19]

The most common secondary outcomes included the rate of IMV or escalation of respiratory support,[2,21] ICU length of stay,[2,23] hospital length of stay,[2,21-23] respiratory rate[2,18,23] and heart rate.[18,23] Patient discomfort or tolerability was assessed in three studies using a 0 to10 scale,[2,21] where 10 was the most comfortable, or 1 to 5 scale,[18] where one was the most comfortable. The severity of dyspnea was also measured using a 0 to 6 scale[2] or a 0 to10 scale,[2,21] with six and 10 being most severe, respectively.

**Cost-Effectiveness studies**

The outcomes evaluated in the cost study were the cost per intubation/re-intubation averted and the total cost-saving per patient with nasal high flow therapy.[25]

## Summary of Critical Appraisal

A full description of the critical appraisal is available in Appendix 3.

### *Systematic reviews*

All systematic reviews searched at least three databases and had comprehensive search strategies. Two reviewers independently undertook title and abstract screening in seven systematic reviews,[4,11-14,16,17] minimizing the risk that relevant articles were missed or that irrelevant articles were included. In one of these, it was unclear whether two authors also independently extracted information from the articles,[13] but the others declared that this was the case, such that errors in extraction were less likely. In the remaining study, the number of reviewers involved in screening and extraction was unclear,[15] increasing the risk of errors.

Three reviews did not have any language restrictions,[4,14,16,17] one included studies in English, Spanish, French, and Portuguese,[12] two were restricted to English[11,13] and one did not specify.[15] Further, the latter review did not specify search dates, a clear study question, or exclusion/inclusion criteria for the retrieved studies,[15] lowering its overall quality because it is not clear that the search and extraction would be objective and reproducible.

Two reviews did not describe assessment of publication bias[4,15] and one of these also did not assess individual articles' risk of bias.[15] The remaining reviews planned publication bias assessment though two did not ultimately undertake it due to too few publications.[11,17] Where it was measured, publication bias demonstrated whether studies with null findings may not have been published, potentially biasing the overall evidence base. Risk of bias assessment was planned in seven studies using the Cochrane tool,[4,11-14,16,17] enabling the review authors to judge on the quality of the included evidence in addition to the quantity.

Meta-analysis was planned in all the systematic reviews. Heterogeneity was assessed using the $I^2$ statistic or a Chi-square test in five studies.[4,11-14,16] While the statistic was significant for at least one outcome in each study, random effects models were used to pool heterogeneous results in the six reviews,[4,11-14,16] which helps to ensure study-level differences are accounted for. Of the remaining two reviews, one did not identify any articles despite planning heterogeneity assessment,[17] while the other did not undertake any testing for heterogeneity and pooled results using simple averaging of study effects without comment on potential heterogeneity.[15] This method may have caused results to appear statistically significant because of underestimating the variance, rather than because there was a true effect.

*Randomized studies*

The investigators and patients were not blinded to the treatment allocation in any of the studies because the nature of the treatment and intervention devices precluded it. One study blinded data analysts to the treatment group, which could help reduce the potential that analysts may have treated the data differently depending on the group, biasing the results.[21] Five studies described appropriate strategies for allocation concealment,[2,18,20,22,24] reducing the potential, however these strategies were unclear in the remaining studies.[19,21,24]

Randomization was successful as evidenced by similar baseline characteristics in five studies,[2,20-23] reducing the risk that the observed effect could be confounded by individuals' characteristics. In one study, the treatment group had on average significantly lower body weight, more underlying diseases and a higher respiratory score, but the authors adjusted for these in the final analysis.[24] The two randomized crossover studies did not provide comparisons of subjects based on their assigned order of treatment.[18,19] It is thus possible that any detected effects could be the result of subjects' different characteristics at baseline rather than the intervention.

There was mixed evidence that studies had adequate power to detect an effect, and the scales used to assess certain outcomes in the studies were not validated. Three studies demonstrated large enough sample sizes with power calculations.[2,18,21] One pilot trial did not have a power calculation as it was using the study to inform the future power calculations,[20] while the other pilot trial was underpowered.[22] Two studies did not mention a power calculation,[23,24] and the remaining study based their sample size on previous studies but did not report an associated power to detect an effect.[19] In these studies, it is thus possible that the sample size was too small to detect a significant effect even if it was there. Where scales were used to assess outcomes such as patient comfort, dyspnea or tolerance, none of studies reported on psychometric properties or referred to accepted scales in the field.[2,15,21]

Where reported, patient exclusions did not raise concerns for selection bias. Four studies stated reasons for exclusion in line with study-specific exclusion criteria.[20-22,24] A multi-centre trial did not have exclusion reasons available from all centres but was mostly able to report them.[2] One study did not have clear exclusion criteria, though it did still state reasons for exclusion,[18] while another had exclusion criteria but it did not describe the subsequent reasons for exclusion.[19] The latter study also did not provide a PRISMA flow chart,[19] and, along with one of the pilot trials,[20] did not have clear *a priori* primary or secondary outcomes.

In relation to the statistical analyses, three studies reported precise p-values,[2,23,24] and one reported confidence intervals (CI),[21] while another did not report precise p-values or confidence intervals.[18] Special methods such as bootstrapping,[21], mixed effect models,[2,18,24] paired sample tests[22] or adjusted p-values[23] were employed to account for repeat measures/correlated data in six of the studies as appropriate to ensure significance testing was valid. The statistical methods were not described in detail in one study,[20] and there was no evident p-value adjustment for multiple testing or other special method employed in the remaining study.[19] While presenting results, one study only described select results in text without a table making its findings on some of the declared outcomes unclear.[24] One randomized cross-over study did not declare a washout period between treatment phases, which may have lessened the ability to isolate the effect.[19]

### *Cost-effectiveness studies*

The justification for the cost study's main assumptions, including a five-year device lifetime and no set-up cost for standard oxygen therapy, were unclear, though the assumptions were clearly described. The study used National Health Service reference costs to determine the costs of respiratory failure with/without intubation and costs of complications and considered costs of consumables, thus accounting for a wide variety of costs. The parameter values were derived from RCTs and the confidence interval bounds were used as bounds to conduct sensitivity analyses. The sensitivity analysis was thus grounded in the literature and demonstrated the robustness of their results. The study did not consider longer term costs such as life-years or clearly describe the time horizon.[25]

## Summary of Findings

A full description of the findings is available in Appendix 4.

### *Clinical effectiveness of heated, humidified, high flow oxygen*

#### Need for invasive mechanical ventilation

The need for IMV or intubation may depend on the nature of the patients given NHF compared to COT and the length of therapy, though results were mixed. A systematic review of people who were immunosuppressed retrieved six studies with a pooled result suggesting no difference between the groups (Risk Ratio [RR] = 0.90, 95% CI 0.78; 1.03).[4] Similarly, a randomized study of people who were immunosuppressed found that NHF did not result in lower intubation rates (Hazard Ratio [HR] = 0.85, 95% CI 0.68; 1.06).[2] Two systematic reviews with a general ARF population suggested the risk of IMV or intubation with NHF was significantly lower,[11,16] though two did find a significant difference.[12,15] One systematic review found that NHF was beneficial against COT to reduce the risk of intubation specifically if administered for more than 24 hours (NHF > 24 hours: RR= 0.71; 95% CI, [0.53 to 0.97] versus NHF < 24 hours (RR= 1.24 [95% CI, 0.31 to 4.93]).[14] None of the six systematic reviews that studied this outcome found a significant difference in intubation or IMV in NHF vs NIV,[4,11,12,14-16] and neither did the pilot clinical study assessing NHF vs helmet CPAP.[20]

#### Mortality

Mortality rates were not significantly different between NHF and COT in four systematic reviews,[4,12,14,15] including the one with the longest time period of 28 days.[4] Two clinical studies assessed mortality in NHF versus COT. One found one (0.8%) death in the NHF group and none in the COT group during the seven-day follow up,[21] while the other found no difference in hospital or ICU mortality within 28 days.[2] Similarly, hospital or ICU mortality

did not significantly differ when comparing NHF to NIV in four systematic reviews.[4,12,15,16] One clinical pilot study also did not find a significant difference between hospital or ICU mortality in NHF versus helmet CPAP.[20]

**Length of ICU and hospital stay**

Length of ICU or hospital stay was also found to be similar between NHF and COT or NIV groups in the systematic reviews and clinical studies. Two systematic reviews[15,16] found no significant difference in the intervention groups compared to COT or NIV. Three clinical studies, including the one restricted to people who were immunosuppressed,[2] also did not find a significant difference in NHF compared to CPAP in length of hospital stay[20] or COT.[2,21] However one pediatric study of participants with bronchiolitis did find that the average lengths of ICU (3 versus 4 days; $P < 0.001$) and hospital (4 vs 5 days $P < 0.001$) stays were significantly lower in the NHF group compared COT delivered through an OxyMask.[23]

**Oxygenation**

Improvement in markers for oxygenation in NHF compared to COT was mixed in the systematic reviews and clinical studies. One review found no significant difference in oxygen saturation, though $PaO_2$ was significantly lower with NHF (104.5 vs 90.0 mm Hg; $P = 0.04$).[15] Two clinical studies did not find a significant difference in $SpO_2$,[18,21] while two other studies did not find a significant difference in the $PaO_2$:$FiO_2$ ratio.[19,22] One randomized crossover study found $PtCO_2$ at 30 minutes was significantly lower in NHF (MD = −1.4 mm Hg [95% CI −2.2 to −0.6]).[18] Relative to NIV, one systematic review found the impact on $PaO_2$ was inferior with NHF at 30 minutes post-intervention in two retrieved studies,[12] though another review found significantly better $PaO_2$ (106.9 vs 134.2 mm Hg, $P = .020$) and $PaCO_2$ (37.7 vs 39.2 mm Hg, $P = .043$) with NHF.[15] A pediatric bronchiolitis study found treatment failure, partly defined as $FiO_2 < 0.5$, was significantly lower in NHF versus COT (OR = 0.15 [95% CI 0.03; 0.66]).[23]

**Dyspnea and patient comfort**

Dyspnea and patient comfort was similar or potentially better with NHF compared to COT or NIV, though these outcomes were less studied. One systematic review found four studies each reporting significantly reduced or no significant difference in dyspnea using NHF versus COT.[13] One review found marginally improved dyspnea (score 2.7 versus 4.3; $P = 0.046$),[15] while neither of two randomized studies found a significant difference.[2,21] Patient comfort assessed using a visual analogue or Likert scale was found to be significantly better with NHF in one systematic review when compared to face mask of NIV. The same review found that NHF was rated as more tolerable than COT.[13] Another review did not find a difference in comfort scores with NHF compared to COT.[15] One randomized study found similar visual analogue scale scores in NHF versus COT,[2] while another randomized study found it was higher with NHF (mean difference on 0-10 scale –1.8 [95% CI –2.4 to –1.1]).[21]

**Adverse events**

Few systematic reviews or clinical trials reported on adverse events. One systematic review found no difference in pneumothorax in NHF (n = 8; 1.95%) versus NIV (n = 7; 1.7%). Two studies reported patient intolerance to NHF that required discontinuation in 12 (3%)[2] and 1 (0.04%) patient,[18] respectively. Another randomized study found the most common cause of treatment failure was persistent tachycardia and increased used of oxygen, but this did not differ across treatment groups.[23]

One systematic review did not find any studies comparing NHF to continuous or bilateral positive airway pressure in pediatric patients without bronchiolitis and thus did not report on any outcomes.[17]

*Cost-Effectiveness*

The included cost-effectiveness study found that nasal high flow therapy dominated (i.e. lower cost and greater effectiveness) COT (-469 £) and NIV (-611 £). The effectiveness outcome was averted intubations.[25] The results were robust to several sensitivity analyses.

*Guidelines*

There were no relevant evidence-based guidelines identified.

### Limitations

None of the studies could be blinded, thus is it possible that underlying differences between intervention and comparison groups may be biased by knowledge of the treatment group. At the same time, outcomes assessors and data analysts were also not generally blinded. This blinding would have been possible to reduce the potential that data from the intervention and control groups were treated differently, creating a bias in the results. This limitation was also noted in one of the systematic review.[12]

The systematic reviews that conducted bias and quality assessment generally reported good ratings for the included studies.[4,11-14,16] However, some also highlighted heterogeneity across primary studies.[4,14] The inconsistency, along with lack of blinding, led to a GRADE evidence rating of 'low quality' in one systematic review.[13] Despite the use of random effects models in meta-analysis, it is still possible that outcomes are not directly comparable. Publication bias was not detected in the systematic reviews that measured it.

The only systematic review relevant to a pediatric population was conducted based on studies up till 2013; it did not retrieve any studies at that time. We also did not find studies assessing subjects during hospital transfers, or any evidence based guidelines on NHF.

## Conclusions and Implications for Decision or Policy Making

The evidence base for this rapid review comprises eight systematic reviews, eight randomized clinical studies, and one cost-effectiveness study to determine the clinical and cost-effectiveness of heated, humidified high flow oxygen. Recently, as highlighted in this evidence review, there has been a proliferation of evidence on the question of clinical effectiveness. However the proliferation of cost-effectiveness studies has not followed. No included study addressed the use of NHF during hospital transfers.

The evidence identified in this review was mixed in terms of whether there was clinical benefit associated with nasal high flow oxygen relative to conventional oxygen therapy or non-invasive respiratory support. Studies of patients who are immunosuppressed did not find a difference in intubation rates, though other systematic reviews and studies were mixed, potentially suggesting benefit to avert intubation. At the same time, the evidence did not generally find a difference in mortality, length of hospital stays, or markers for oxygenation improvement. There is some suggestion that patient comfort may be improved, however this outcome was not systematically addressed across the studies.

The systematic reviews generally had a low risk of bias, however the randomized clinical trials were more mixed. The main risks of bias in the clinical trials stemmed from small

sample sizes, unclear primary outcomes and lack of blinding. Non-neonatal pediatric clinical trials were lacking relative to adult studies, making the effectiveness of NHF in this population less clear. The one cost-effectiveness study demonstrated NHF was superior for both cost- and clinical effectiveness to avert intubations. It was however it was completed in a UK setting, and while the clinical benefit may transfer, the costs may be less applicable in Canada.

Future research considering cost-effectiveness in Canada, including on the training and health care resources that may be required to use heated, humidified high flow oxygen therapy for acute respiratory failure, may provide more clarity on this intervention's cost-effectiveness. In addition, studies of non-neonatal pediatric populations and during hospital transfers could help clarify whether NHF is beneficial in these groups.

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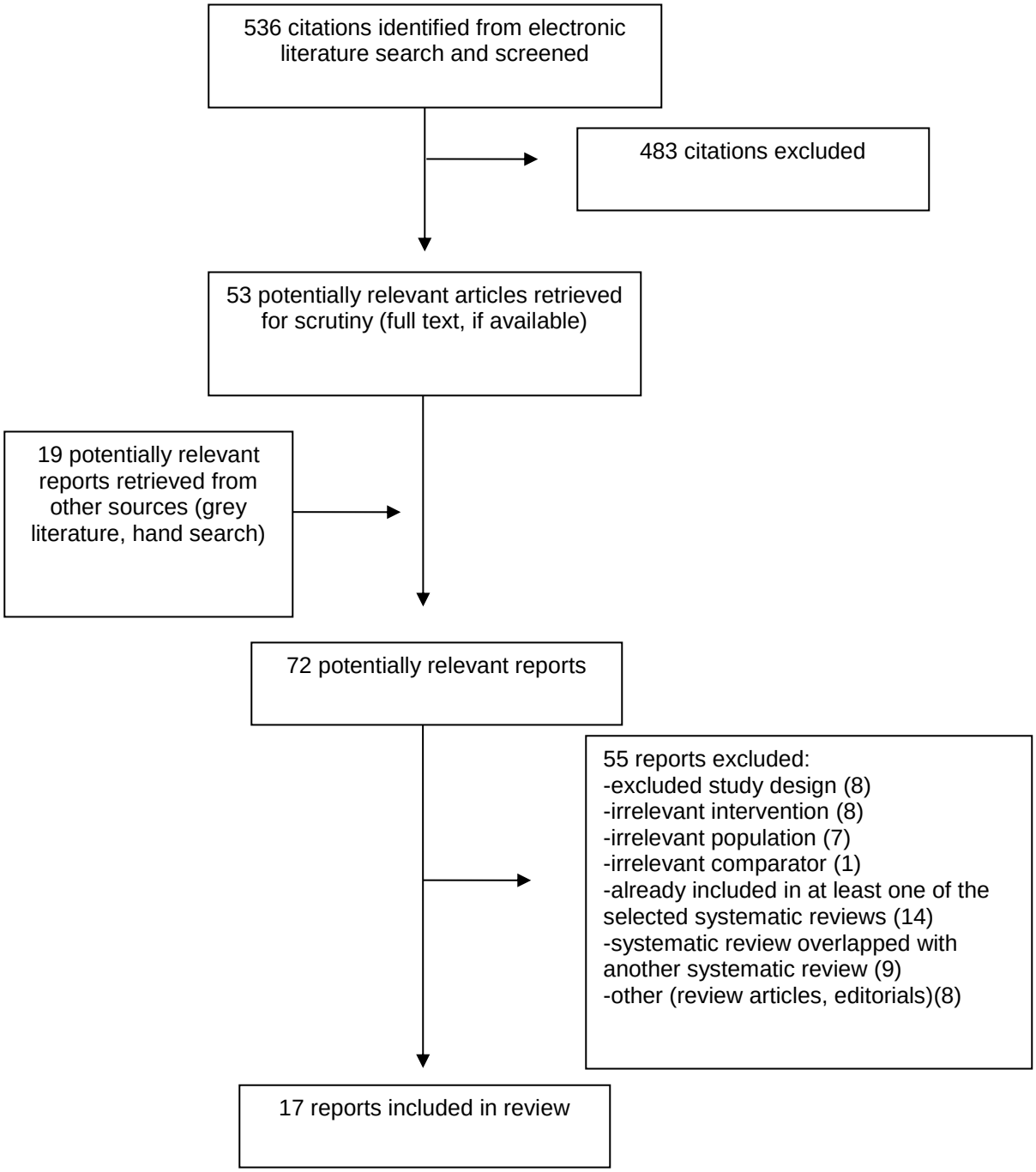
## Appendix 1: Selection of Included Studies



# Appendix 2: Characteristics of Included Publications

## Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

| First Author, Publication Year, Country | Study Designs and Numbers of Primary Studies Included | Population Characteristics | Intervention (I) and Comparator(s) (C) | Clinical Outcomes |
|---|---|---|---|---|
| **Sklar, 2018, Canada**[4] | Four RCTs, eight retrospective observational studies and one prospective observational study reporting on 1,956 subjects | Immunocompromised adults undergoing NHF for ARF | (I) NHF through nasal cannulae<br>(C) NIV or COT delivered through any means | Primary: mortality at the longest available time point<br>Secondary: rate of invasive mechanical ventilation |
| **Liesching, 2017, USA**[15] | 18 studies including 11 RCTs and 7 prospective comparative studies, with 2,087 patients | Adult patients (not further specified) | (I) NHF oxygen therapy<br>(C) Standard therapy (not further specified, though all studies compared to COT or NIV) | Primary and secondary outcomes not specified (see results) |
| **Monro-Somerville, 2017, UK**[13] | Fourteen RCTs including 2,507 subjects. | Adult patients with respiratory failure of any cause | (I) NHF through nasal cannulae<br>(C) 'Usual Care', i.e. any other mode of oxygen delivery including COT (i.e., conventional facemask or nasal cannula) and NIV | Primary: Hospital mortality rate<br>Secondary: Endotracheal intubation<br>Qualitative assessment of patient tolerability and comfort |
| **Nedel, 2017, Brazil**[12] | 9 RCTs (did not report total number of subjects) | Adults who are critically ill with AHRC or at risk for this complication | (I) HFNC treatment<br>(C) COT or NIV | Primary: Intubation rate<br>Secondary: Improvement in $PaO_2$:$FiO_2$, mechanical ventilation time and ICU mortality |
| **Ni, 2017, China**[16] | 12 RCTs, four retrospective analyses and two prospective cohort studies with 3,881 patients | Adults aged 18+ with ARF (respiratory rate > 25 breaths/min with oxygen index < 300 mmHg or arterial oxygen saturation < 92% with 10 to 12 L/min of $O_2$ or < 94% on room air) | (I) NHF oxygen therapy<br>(C) NIPPV or COT | Rate of endotracheal intubation, ICU mortality, and length of stay |
| **Ou, 2017, China**[11] | Six RCTs with 1,892 patients | Adults aged 16 plus in the ICU with ARF | (I) NHF oxygen therapy at a flow rate greater than 15 L/min<br>(C) COT with delivery by nasal cannula or mask; NIV using a face mask connected to an ICU ventilator | Primary: Endotracheal intubation rate<br>Secondary: $PaO_2$:$FiO_2$, $PaCO_2$, arterial pH, respiratory rate, mortality in ICU, length of ICU stay and ventilator-induced lung injury |

| First Author, Publication Year, Country | Study Designs and Numbers of Primary Studies Included | Population Characteristics | Intervention (I) and Comparator(s) (C) | Clinical Outcomes |
|---|---|---|---|---|
| **Zhu, 2017, China**[14] | Four RCTs with 703 patients (n = 371 in HFNC group and n = 332 in COT group) | Adult patients with ARF, however defined by the studies | (I) NHF through nasal cannulae<br>(C) COT through nasal prongs, facemasks or Venturi masks | Primary: rate of escalation of respiratory support<br>Secondary: intubation rate, mortality at longest follow up, transfers to ICU and complications |
| **Mayfield 2014, Australia**[17] | None (restricted to RCTs and quasi-RTs) | Patients aged 4 weeks to 16 years requiring respiratory support for type 1 and 2 respiratory failure, parenchymal lung disease, neuromuscular disorders, respiratory drive and airway obstruction, excluding children with bronchiolitis. | (I) NHF therapy (defined as the delivery of heated, humidified oxygen or blended oxygen with air via nasal cannula at flow rates greater than 2 L/min)<br>(C) COT, hood or tent oxygen; low-flow nasal cannulae (flow rates ≤ 2 L/min); and continuous positive airway pressure or bi-level positive airway pressure delivered via facial or nasal mask/cannula | Primary outcomes: Hospital mortality, intubation rate, treatment failure<br>Secondary outcomes: Hours of respiratory support required, hospital length of stay, clinical severity score, PICU length of stay, complications |

ARF=Acute Respiratory Failure; CO2=Carbon Dioxide; COT=Conventional Oxygen Therapy; FiO2=Fraction of Inspired Oxygen; HFNC=High flow Nasal Cannulae; ICU=Intensive Care Unit; NHF=Nasal High Flow; NIPPV = Non-Invasive Positive Pressure Ventilation; NIV=Non-invasive ventilation; O2=Oxygen; PaO2=Partial Pressure of Oxygen; PICU=Pediatric Intensive Care Unit; RCT=Randomized Controlled Trial

## Table 3: Characteristics of Included Primary Clinical Studies

| First Author, Publication Year, Country | Study Design | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| **Azouley, 2018, France,**[2] | Multi-centre, open, parallel-group RCT at 32 hospitals in France | Age: Adults aged 18<br>Condition: Immunosuppression (steroid use > 3 months, other immunosuppressant drugs, solid organ transplantation, solid tumor requiring chemotherapy in the last 5 years, hematologic malignancy or primary immune deficiency) and admitted to the ICU with AHRF ($PaO_2$ < 60 mm Hg, $SpO_2$< 90%, tachypnea > 30/min, laboured breathing/respiratory distress, need for oxygen flow > 6 L/min)<br>Exclusion criteria: 1) diagnosis of Acquired Immune Deficiency Syndrome; 2) imminent death; 3) participation refused; 4) anatomical factors precluding the use of a | (I) Continuous high flow oxygen initiated at 50 L/min and 100% FiO2, and up to 60 L/min to achieve $SpO_2$ of ≥95%.<br>(C)COT delivered via any device with flow maintained to achieve SpO2 of >= 95% | Primary: Mortality<br>Secondary: need for invasive mechanical ventilation, respiratory rate, lowest $PaO_2$:$FiO_2$ ratio , patient comfort score (0-10, 10 being highest), dyspnea score (0 to 10 with 10 being worse), ICU and hospital lengths of stay, ICU-acquired infections<br>Follow up: 28 days |

| First Author, Publication Year, Country | Study Design | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| | | nasal cannula; 5) hypercapnia ($PaCO_2$ ≥50 mm Hg); 6) isolated cardiogenic pulmonary edema indicating NIV;7) pregnancy or breastfeeding; 8) No French statutory health insurance; 9) surgery within last six days | | |
| **Ballestero, 2018[22]** | Single-centre, open RCT (pilot study) | Age: Children aged 1 to 14<br>Condition: Moderate to severe asthma exacerbations (one of pulmonary score >=6, $SpO_2$ < 94%)<br>Exclusion criteria: 1) Required advanced airway management; 2) No informed consent and those in whom informed consent was not obtained were excluded. | (I) NHF with flow rate 2 to 25 L/min for infants/young children and 5 to60 L/min for older children/adolescents, which varied depending on patient weight and clinical status.<br>(C) COT delivered any device, depending on the patient's level of distress and oxygen requirement. | Primary: change in asthma severity (decrease in pulmonary score by ≥ 2 points in the first 2 hours of treatment)<br>Secondary: admission rate to the PICU or ward; length of stay; the need for additional therapies as determined by the treating physician, specifically inhaled salbutamol, corticosteroids, or intravenous magnesium sulfate; and additional respiratory support.<br>Follow up: Every 30 minutes during the first 2 hours and then every 2 hours until the decision for disposition, followed by phone call at 72 hours. |
| **Ergul, 2018, Turkey, [23]** | Single-centre, open, RCT | Age: 1 to 24 months<br>Condition: Moderate to severe acute bronchiolitis and admitted to the ICU.<br>Exclusion criteria: 1) Need for immediate respiratory support; 2) already admitted to the ICU due to respiratory failure; 3) underlying chronic lung disease or cardiovascular disorders; 4) upper respiratory tract obstruction; 5) cranial malformations | (I) NHF using Precision Flow nasal cannula, with initial flow rate 1 L/kg/min up to 20 L/min and maximum $FiO_2$ of 60%. $FiO_2$ was decreased to 20% after, and therapy stopped when $PaO_2$ was maintained at 94% for more than 4 hours.<br>(C) COT delivered through an OxyMask with flow rate 10-15 L/min to maintain $SpO_2$ of at least 94%; the flow rate was decreased to 2 L/min, and therapy stopped if $SpO_2$ maintained at 94% for more than 4 hours | Primary: Failure rate (2/3 No change or increase in respiration rate, no change or increase in heart rate, persistence of low $SpO_2$ < 92%)<br>Secondary: time to weaning off oxygen therapy or lengths of hospital and ICU stays, respiration and heart rates, pH, $PaCO_2$ or $SPO_2$ |
| **Ramnarayan, 2018, UK[20]** | Multi-centre, open RCT (pilot study) | Age: > 36 weeks and < 16 years old<br>Condition: requiring non-invasive respiratory support for acute illness ($PaO_2$ | (I) NHF<br>(C) Continuous positive airway pressure delivered using helmet, | -Not stated a priori<br>-Follow up 28 days |

| First Author, Publication Year, Country | Study Design | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| | | < 92% or respiratory acidosis (pH < 7.3) or moderate respiratory distress<br>Exclusion criteria: 1) required immediate intubation/invasive ventilation; 2) current tracheostomy; 3) pre-existing air-leak syndrome; 4) mid-facial/craniofacial anomalies or recent craniofacial surgery; 5) 'not for intubation' order; 6) had domiciliary ventilation ; 7) already managed with NIV within 24 hours; 8) previously recruited to the study; or 9) unavailability of NIV. | nasal prong or mask as per usual protocol | |
| **Sitthikarnkha, 2018, Thailand[24]** | Single-centre, open, RCT | Age: 1 month to 5 years<br>Condition: Admitted to general pediatric ward or PICU with respiratory distress (high RR, increased work of breathing or oxygen saturation < 95%)<br>Exclusion criteria: 1) Require immediate mechanical ventilation; 2) hemodynamic instability; 3) congenital cyanotic heart diseases; 4) air leak syndrome; 5) nasal mucosa injury; 6) or refused to participate . | (I) NHF (MR850 heated humidifier) with $FiO_2$ between 0.2 and 1 and initial flow determined by current weight starting at 6 L/min, to achieve at least 95% $O_2$ saturation.<br>(C)COT delivered through nasal cannula with flow rate 2 L/min, face mask or oxygen box depend on clinical severity with the aim to maintain oxygen saturation >= 95%. | Primary: Treatment failure (does not achieve 2/3: respiratory rate reduction by 20% or to within normal range, heart rate reduction by 20% or to within normal range, and $FiO_2$< 0.5)<br>Secondary: Respiratory parameters<br>Follow up: All parameters were measured at baseline and at 1, 6, 12, 24, and 48 h; then daily |
| **Makdee, 2017, Thailand[21]** | Single-centre, open RCT | Age: Adults aged 18 +<br>Condition: diagnosis of cardiogenic pulmonary edema, pulse oximetry reading < 95%, and RR > than 24 breaths/min.<br>Exclusion criteria: 1) need for immediate intubation or NIV; 2) presence of myocardial infarction; 3) Glasgow Coma Scale score < 13; 4) hemodynamic compromise; 5) pregnancy; 6) respiratory failure or increased work of breathing; 7) SpO2 < 90%; 8) end-stage renal disease; 9) equipment contraindications; 10) concomitant pneumonia | (I) NHF with initial flow rate 35 L/min up to max of 60 L/min, and FiO2 set to maintain $PaO_2$ >= 95% for 60 minutes.<br>(C)COT via nasal cannula or nonrebreather mask with median flow rate 3 L/min. | Primary: Respiratory rate at 60 minutes<br>Secondary: $SpO_2$, pulse rate, blood pressure, severity of dyspnea (evaluated with a visual analog scale ranging from 1 to 10), rate of adverse events (thoracic and cervical discomfort, feeling hot, aspiration, and nasal ulceration), requirement for escalation to intubation or noninvasive ventilation within 24 hours after ED arrival, ED and hospital length of stay, mortality within 7 days, and pulmonary edema grade as determined by chest radiograph findings<br>Follow up: 60 minutes |

| First Author, Publication Year, Country | Study Design | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| | | | | |
| **Mauri, 2017, Italy**[19] | Single centre randomized crossover study | Age: Adult > 18 years old<br>Condition: Admitted to ICU with AHRF lasting < 1 week, $PaO_2$ /set $FIO_2$ <=300 mm Hg<br>Exclusion criteria: 1) intubation or tracheostomy; 2) pregnant or breastfeeding; 3) hemodynamic instability; 4) pneumothorax; 5) acute cardiogenic pulmonary edema; 6) chronic obstructive pulmonary disease; 7) nasal trauma and/or deviated septum; 8) contraindication to EIT; 9) impossibility to position the EIT belt or esophageal pressure catheter | (I) NHF with flow rate 40 L/min for 20 minutes, and $FiO_2$ clinically determined to achieve 90-95% saturation<br>(C)Standard oxygen facemask with flow rate 12 L/min for 20 minutes. | Breathing, Ventilation, Gas Exchange, and Hemodynamics<br>Follow up unclear |
| **Pilcher, 2017, New Zealand**[18] | Randomized controlled cross-over trial | Age: Adults aged 16 and older<br>Condition: Acute exacerbation of chronic obstructive pulmonary disease, and receiving $O_2$ therapy via standard nasal prongs | (I) 15 minutes of standard nasal prong oxygen, followed by administered 30 min of NHF with flow rate 35 L/ min, followed by at least 15-min washout period<br>(C)15 minutes of standard nasal prong oxygen, followed by 30 min of COT via standard nasal prong | Primary: $PtCO_2$ at 30 minutes, adjusted for time 0 measurement<br>Secondary: change in $PtCO_2$, respiratory rate, heart rate, $PtCO_2$ and $SpO_2$<br>Follow up: Observed every 5 minutes until end of washout/observation period |

AHFR= Acute hypoxemic respiratory failure; Conventional Oxygen Therapy; ED = Emergency Department; EIT=Electrical Impedance Tomography; FiO2=Fraction of Inspired Oxygen; HFNC=High Flow Nasal Cannulae; IQR=Interquartile range; NHF=Nasal High Flow; NIV=Non-invasive ventilation; PICU=Pediatric Intensive Care Unit; PtCO2 =transcutaneous carbon dioxide tension; $SpO_2$= Pulse Oximetry; 95% CI=95% Confidence Interval

## Table 4: Characteristics of Included Economic Evaluations

| First Author, Publication Year, Country | Type of Analysis, Perspective | Intervention, Comparator | Study Population | Time Horizon | Main Assumptions |
|---|---|---|---|---|---|
| **Eaton Turner, 2017, UK**[25] | Scenario: First-line therapy<br>Model: Decision analytic model run based on 100 patients using the proposed therapy per year, assuming a 5-year lifetime of the device<br>Perspective: UK NHS | Optiflow nasal high flow vs COT using nonrebreather face mask or NIV using face mask and ICU ventilator | ICU patients who have acute respiratory failure and have not previously undergone endotracheal intubation | Limited to the time horizon used in the three RCTs used to inform the parameters | -Five year lifetime for device<br>-The cost was the weighted cost of respiratory failure without intubation from the cost of respiratory failure with intubation<br>-The cost of AIRVO™ NHF device based on 28 patients using the device each year 5 years<br>-No set-up cost for standard oxygen therapy<br>-Costs based on NHS reference costs |

COT = Conventional Oxygen Therapy; ICU = Intensive Care Unit; NHS = National Health Service; NIV = Non-invasive Ventilation, RCT = Randomized Controlled Trial;

# Appendix 3: Critical Appraisal of Included Publications

## Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[7]

| Strengths | Limitations |
|---|---|
| Sklar, 2018[4] | |
| -Two reviewers determined article eligibility, with conflicts resolved through consensus<br>-Two reviewers abstracted the data independently<br>-Source of bias assessment using Cochrane Collaboration Risk of Bias Tool and Newcastle-Ottawa Scale<br>-Searched six databases with no time or language restrictions<br>-Used random effects models to pool across studies<br>-Measured heterogeneity using $I^2$ statistic<br>-Clear description of PICO criteria<br>-Assessed risk of bias in meta-analysis by excluding observational studies; did not impact results | -No reference to pre-published protocol, though search strategy was online<br>-Did not investigate publication bias<br>-Did not describe excluded studies |
| Liesching, 2017[15] | |
| -Searched three databases | -Did not specify search dates<br>-Did not specify inclusion/exclusion criteria for articles<br>-Did not specify clear PICO criteria<br>-Did not state number of authors involved in abstract screening, extraction<br>-No quality or bias assessment<br>-No measure of study heterogeneity or modelling strategy to compensate for this (simple averaging of study effects) |
| Monro-Somerville, 2017[13] | |
| -Pre-published systematic review protocol<br>-Searched three databases<br>-Search was conducted independently by two authors with conflicts resolved by consensus of all authors<br>-Bias assessment using Cochran risk of bias tool<br>-Used GRADE to assess the quality of evidence including inconsistency, indirectness, imprecision, and publication bias<br>-Assessed study heterogeneity using $I^2$ and used random effects model and Trial Sequential Analysis to pool results as appropriate<br>-Reported reasons for excluding studies which included not reporting relevant outcomes, use of healthy volunteers and use of HFNC during airway instrumentation | -Few studies for publication bias assessment so difficult to interpret<br>-No reference to a published protocol |
| Nedel, 2017[12] | |
| -Study protocol published in PROSPERO<br>-Searched three databases until June 2015 and included four languages<br>-Two authors independently screened, extracted and assessed bias in the articles<br>-Bias was assessed using Cochrane risk of bias tool<br>-Heterogeneity assessed using chi-square test and Higgins inconsistency test<br>-Publication bias assessed using funnel plots<br>-Results pooled using random effects model | -Limited to English language<br>-Unclear whether two authors independently extracted data or assessed study quality<br>-Unclear search dates<br>-Stated that crossover studies were excluded however included 5 crossover studies<br>-Used ORs which may overestimate RRs because the outcomes were common |

| Strengths | Limitations |
|---|---|
| Ni, 2017[16] | |
| -Searched five databases from 1946 to October 2016<br>-Two reviewers independently screened titles/abstracts and reviewed full texts with disagreements resolved by consensus<br>-Two reviewers independently extracted articles<br>-Cochrane risk of bias tool used to assess study quality, conducted by two investigators<br>-Heterogeneity assessed using Chi-Squared test and $I^2$ value<br>-Results pooled using random effects models<br>-Explained reasons for excluded studies<br>-Assessed publication bias using funnel plot | -Reported odds ratio which may exaggerate the corresponding risk ratio<br>-Did not comment on low quality of one of the studies (but did not include in meta-analysis either) |
| Ou, 2017[11] | |
| -Searched five databases from inception until April 18, 2016<br>-Two reviewers independently extracted the studies, with disagreements resolved by consensus<br>-Risk of bias was assessed using the Cochrane risk of bias tool<br>-Data pooled using random effects model, with heterogeneity assessed using $I^2$ and chi-square tests<br>-Provided details on excluded studies | -Did not specify any language restrictions<br>-Reported odds ratio which may exaggerate the corresponding risk ratio |
| Zhu, 2017[14] | |
| -Searched four databases until June 2016 without limitations<br>-Two reviewers screened and abstracted articles with disagreements resolved by consensus<br>-Two reviewers assessed risk of bias tool described in Cochrane Handbook<br>- $I^2$ to assess study heterogeneity, with random effects model to pool<br>-Publication bias assessed using a funnel plot<br>-Described reasons for exclusion | -Restricted language to English<br>-Unclear whether two reviewers also screened the titles and abstracts<br>-No publication bias assessment because not enough studies |
| Mayfield, 2014[17] | |
| -Searched five databases, and for relevant unpublished trials, and hand searched from included studies<br>-No language or year restrictions<br>-Two authors independently screened articles<br>Followed standard methodological procedure by Cochrane Collaboration | None |

GRADE = Grading of Recommendations, Assessment, Development and Evaluations; PICO = Population, Intervention, Comparator, Outcome

## Table 6: Strengths and Limitations of Clinical Studies using Downs and Black[8]

| Strengths | Limitations |
|---|---|
| Azoulay, 2018[2] | |
| -Pre-published protocol<br>-Randomization using an electronic system linked to case report form<br>-Allocation concealment achieved through permutation blocks with size of 4, which was concealed<br>-Power calculation described and sample size adequate<br>-Appropriate statistical analysis using Cox model with verification of the proportional hazards assumption, as well as risk difference<br>-Clear description of all statistical methods employed and | -No blinding for outcomes assessment<br>-Reasons for exclusion not available from all centers |

| Strengths | Limitations |
|---|---|
| provided precise p-values<br>-Both relative and absolute measures were derived<br>-ITT approach<br>-Successful randomization evidence from baseline characteristics<br>-Assessed centre effects (no significant effect on mortality or intubation rate) | |
| Ballestero, 2018[22] | |
| -Published study protocol<br>-Clear research question and description of intervention and comparator treatments<br>-Allocation concealment achieved using sequentially numbered opaque envelopes<br>-Provided table of baseline characteristics which were similar across groups<br>-Used paired samples test to compare measures at baseline and different time points<br>-Description of reasons for patient exclusion | -Described power calculation, though since it was a pilot trial they were not expecting to recruit fully (required 338 patients for 80% power at 5% significance, but expected to recruit 50 to 100)<br>-Conducted univariate analysis for each clinical variable but did not adjust p-value |
| Ergul, 2018[23] | |
| -Clear hypothesis, main outcomes well-described<br>-Provided table of patient baseline characteristics with no evidence of important differences<br>-Intervention and comparator treatment described clearly<br>-Reported precise p-values<br>-Reported means and standard deviations, and test for normality | -Did not give specific reasons for patient exclusions<br>-Did not report on any significant events or side effects<br>-no blinding or allocation concealment reported<br>-more severe patients may have been excluded since immediate requirement for O2 was an exclusion criteria, however this is not expected to be different across treatment groups<br>-no power calculation<br>-did not used mixed effects regression to determine changes from baseline, though adjusted the p-value |
| Ramnarayan, 2018[20] | |
| -Published study protocol<br>-Allocation concealment achieved through computer generated randomization with variable block sizes<br>-ITT statistical analysis<br>-described reasons for exclusion<br>-provided table of baseline characteristics which were comparable across groups<br>-Provided relative and absolute measures | -treatment not blinded (not possible)<br>-did not describe intervention and comparator in detail<br>-pilot RCT, thus no formal power calculation<br>-Likely underpowered (as stated by the authors)<br>-lack of detail on statistical methods<br>-lack of a priori clinical outcomes (as the study was being used to inform a larger RCT) |
| Sitthikarnkha, 2018[24] | |
| -Clear research question with outcome criteria well-described<br>-Patient characteristics provided with differences highlighted<br>-Intervention and comparator treatment described clearly<br>-Reported precise p-values<br>-Described reasons for excluding subjects<br>-Allocation concealment through opaque sealed envelopes generated by computerized fixed block method<br>-Appropriate statistical analysis controlling for the confounding factors present at baseline, and mixed effects regression to determine changes in physiologic variables | -Baseline differences with NHF group having lower average body weight (8.3 +/- 3.1 vs 9.9 +/- 2.2, p = 0.01), more underlying disease ( p = 0.036) and a higher respiratory score (9 +/- 1.1 vs 8.1 +/- 1.1; p < 0.001)<br>-treatment not blinded (likely not possible)<br>-Did not report a table of results , and limited text presentation to only select results<br>-No power calculation |
| Pilcher, 2017[18] | |
| -Randomization through computer-generation<br>-Allocation concealment through sequentially numbered opaque envelopes (did not describe block size if any)<br>-Described power calculation which was able to detect 2.4 mm | -Did not define chronic obstructive pulmonary disease exacerbation or diagnostic criteria<br>-Did not describe exclusion criteria<br>-The duration or intensity of oxygen therapy prior to the study |

| Strengths | Limitations |
|---|---|
| Hg difference in PtCO2 (though this was not the primary outcome)<br>-Appropriate statistical analysis using random effects to account for repeat measures on participants<br>-ITT analysis<br>-Study was prospectively registered as a trial | was not assessed in baseline characteristics<br>-Did not describe tolerability outcome in the methods, and measure was not a known validated measure<br>-Did not present precise p-values |
| Makdee, 2017[21] | |
| -Clear research question and hypothesis<br>-Described reasons for exclusion<br>-Blinding of data analyst<br>-ITT analysis except excluded patients who were subsequently determined not to meet the inclusion criteria (2 in COT and 5 in NHF)<br>-Appropriate statistical analysis including median differences with bootstrap confidence intervals<br>-Power calculation suggested adequate sample size<br>-Similar baseline characteristics suggest successful randomization | -Did not describe randomization or allocation concealment strategies<br>-No reference to pre-published protocol<br>-No reference to ethics approval |
| Mauri, 2017[19] | |
| -Computer randomization of order of treatment delivery<br>-Clear research question | -Does not clearly state primary outcomes<br>-No allocation concealment<br>-No washout period described between treatments<br>-Sample size chosen based on previous studies but did not declare power<br>-Did not adjust p-value for multiple testing<br>-No PRISMA flow chart describing exclusions<br>-No evident trial registration |

COT = Conventional Oxygen Therapy; ITT = Intention –to-treat; NHF = Nasal High Flow; $O_2$ = Oxygen; $PtCO_2$ = Transcutaneous carbon dioxide tension

## Table 7: Strengths and Limitations of Economic Studies using the Drummond Checklist[9]

| Strengths | Limitations |
|---|---|
| Eaton Turner, 2017, UK[25] | |
| -Parameter values identified through published literature<br>-Confidence intervals for parameter values informed distribution and ranges for sensitivity analyses<br>-Effectiveness data obtained through RCTs<br>-Described assumptions in detail<br>-Considered costs of consumables as well as healthcare based on NHS reference costs<br>-Conducted deterministic and probabilistic sensitivity analyses showing robust results | -Did not discuss cost of physical units such as physician visits or life years gained except for nurses' time to train on the device<br>-Did not clearly describe time horizon |

NHS = National Health Service; RCT = Randomized Controlled Trial

# Appendix 4: Main Study Findings and Authors' Conclusions

## Table 8: Summary of Findings Included Systematic Reviews and Meta-Analyses

| Main Study Findings | Authors' Conclusion |
|---|---|
| **Sklar, 2018[4]** | |
| **Mortality**<br>NHF vs NIV or COT (7 studies; $I^2$ = 48%; *P* = 0.01);<br>RR = 0.72 (95% CI 0.56; 0.93)<br>NHF vs NIV (4 studies with 545 subjects, $I^2$ = 52%, *P* = .10);<br>RR = 0.60, 95% CI 0.37; 0.97)<br>NHF vs COT (5 studies, with 1,097 subjects; $I^2$= 49%, *P* = .11);<br>RR = 0.80, 95% CI 0.62;1.05)<br>**Need for intubation**<br>NHF vs NIV or COT (8 studies; $I^2$ = 34%; *P* = 0.02);<br>RR = 0.81 (95% CI 0.67; 0.96)<br>NHF vs NIV (4 studies, with 545 subjects; $I^2$ = 68%, *P* = .07);<br>RR = 0.67, 95% CI 0.43;1.04)<br>NHF vs COT (6 studies, with 1,197 subjects; $I^2$= 0%, *P* = .12);<br>RR = 0.90, 95% CI 0.78 ;1.03) | "In our exploratory analysis, we found that mortality and invasive mechanical ventilation were decreased with the use of HFNC compared to any oxygen therapy control (ie, NIV or conventional O2 therapy)" (pg 1563) |
| **Liesching, 2017[15]** | |
| **NHF vs COT (outcomes with at least 2 studies)**<br>-respiratory rate: 1.6 vs 24.7, *P* = .059<br>-heart rate: 89.1 vs 98.4, *P* = .033<br>-oxygen saturation: 95.0% vs 93.8, *P* = .267<br>-$PaO_2$: 104.5 vs 90.0 mm Hg, *P* = .044<br>-$PaCO_2$: 38.3 vs 39.3 mm Hg, *P* = .328<br>-pH: 7.416 vs 7.419, *P* = .898<br>-Dyspnea: 2.7 vs 4.3, *P* = .046<br>-Discomfort score: 1.19 vs 1.44, *P* = .435<br>-Intubation/reintubation: OR = 0.79, 95% CI: 0.39-1.21, *P* = .269<br>-ICU mortality: OR = 0.69, 95% CI: 0.43-1.11, *P* = .126<br>-ICU length of stay: 4.0 vs 4.5 days, *P* = .896<br>**NHF vs NIV (outcomes with at least 2 studies)**<br>-respiratory rate: 1.8 vs 23.6, *P* = .254<br>-heart rate: 97.8 vs 92.4, *P* = .190<br>-Oxygen saturation: 93.6 vs 96.2, *P* = .275<br>-$PaO_2$: 106.9 vs 134.2 mm Hg, *P* = .020<br>-$PaCO_2$: 37.7 vs 39.2 mm Hg, *P* = .043<br>-pH: 7.406 vs 7.396, *P* = .385<br>-Dyspnea: 2.9 vs 2.7, *P* = .547<br>-Discomfort score: 2.22 vs 2.17, *P* = .753<br>-Intubation/reintubation: OR = 0.83, 95% CI: 0.62-1.11, *P* =0.013 | "The most effective outcome is reduced HR and dyspnea, which can be generalized in ICU and CCU. The HFNC modestly reduced ICU mortality and intubation rate" (pg 151) |
| **Monro-Somerville,2017[13]** | |
| **Mortality**<br>-NHF vs 'Usual Care': OR = 0.83 (95% CI 0.58; 1.17);<br>5 studies; $I^2$ = 25%<br>**Intubation**<br>-NHF vs 'Usual Care': OR= 0.69 (95% CI 0.44;1.08);<br>4 studies; $I^2$ = 0%<br>-NHF vs COT only: OR= 0.52 (95% CI 0.36;0.76);<br>8 studies $I^2$ = 35%<br>-NHF vs NIV only: OR = 0.85 (95% CI 0.62;1.17);<br>2 studies; $I^2$ = 58%<br>**Comfort and tolerability** (dyspnea measured using VAS, VNS, 5 point Likert scale and Borg Cr10 scale)<br>-NHF vs 'Usual Care' (two studies): no significantly difference in | "The principal finding of this systematic review and meta-analysis is that no significant difference in mortality or intubation rate was detected in adult patients with ARF treated with HFNC, when compared with usual care defined as COT or NIV. " (pg e454) |

| Main Study Findings | Authors' Conclusion |
|---|---|
| dyspnea<br>-NHF vs facemask (4 studies): significantly reduced dyspnea<br>-NHF vs facemask (5 studies): significantly improved comfort scores<br>-NHF vs NIV (2 studies): significantly improved comfort scores | |
| Nedel,2017[12] | |
| **NHF vs NIV:**<br>-IMV: OR = 0.83 (95% CI 0.57; 1.20); 3 studies, $I^2$ = 22%<br>-ICU mortality: OR = 0.72 (95% CI 0.23; 2.21); 2 studies $I^2$ = 83%<br>**NHF vs COT:**<br>-IMV: OR = 0.49 (95% CI 0.22; 1.08); 5 studies, $I^2$ = 37%<br>-ICU mortality: OR = 0.69 (95% CI 0.33; 1.42); 2 studies $I^2$ = 112% | "This systematic review and meta-analysis suggested that there was no difference in mortality or the need for invasive mechanical ventilation when HFNC is compared with NIV; the same conclusions can be reached when compared with standard oxygen therapy." (pg 130) |
| Ni, 2017[16] | |
| **NHF vs COT:**<br>Endotracheal intubation: OR = 0.47 (95% CI 0.27; 0.84);<br>13 studies; $I^2$ = 34%<br>ICU mortality: OR = 0.65 (95% CI 0.37; 1.13);<br>5 studies; $I^2$ = 0%<br>ICU length of stay: MD, days = 0.30 (95% CI -0.78; 1.37);<br>7 studies; $I^2$ = 0%<br>**NHF vs NIPPV:**<br>Endotracheal intubation: OR = 0.73 (95% CI 0.47; 1.13);<br>6 studies; $I^2$ = 63%<br>ICU mortality: OR = 0.63 (95% CI 0.34; 1.18);<br>5 studies, $I^2$ = 67%<br>ICU length of stay: MD, days = -1.21 (95% CI -3.35; 0.94);<br>5 studies; $I^2$ = 34% | "In the present meta-analysis, we found that HFNC decreased the need for endotracheal intubation in adult patients with ARF, similar to NIPPV. However, HFNC was not associated with improvement in ICU mortality or a decrease in ICU LOS compared with NIPPV and COT." (pg 774) |
| Ou, 2017[11] | |
| **NHF vs COT**<br>Overall Intubation: RR = 0.60 (95% CI 0.38; 0.94);<br>4 studies, $I^2$ = 49%<br>$PaO_2$:$FiO_2$ ratio: MD = 4.72 (-28.90; 38.33); 3 studies; $I^2$ = 90%<br>PaC02 level: MD = -0.40 (-2.54; 1.74); 3 studies; $I^2$ = 71%<br>Arterial pH: MD = 0.00 (-0.03; 0.03); 2 studies; $I^2$ = 37%<br>Respiratory rate: MD = -3.68 (-6.81; -0.55); 2 studies; $I^2$ = 83%<br>ICU mortality: RR = 0.79 (95% CI 0.44; 1.40); 4 studies; $I^2$ = 0%<br>Length of ICU stay: MD = 0.02 (-0.26; 0.30); 3 studies; $I^2$ = 0<br>**NHF vs NIV:**<br>Overall Intubation: RR = 0.86 (95% CI 0.68; 1.09);<br>3 studies $I^2$ = 2%<br>Pa02:Fi02 ratio: MD = -53.84 (95% CI -71.43; -36.24);<br>3 studies; $I^2$ = 44%<br>PaC02 level: MD = -0.53 (95% CI -2.34; 1.28);<br>3 studies; $I^2$ = 62%<br>Arterial pH: MD = 0.01 (-0.00; 0.02);<br>2 studies; $I^2$ = 24%<br>Respiratory rate: MD = -1.13 (-2.01; -0.25);<br>2 studies; $I^2$ = 8%<br>ICU mortality: RR = 0.79 (95% CI 0.31; 2.05);<br>2 studies; $I^2$ = 74%<br>Length of ICU stay: MD = 0.00 (-0.20; 0.20); 2 studies; $I^2$ = 0 | "Our study showed that the proportion of patients with acute hypoxemic respiratory failure who required endotracheal intubation was lower among those who received HFNC oxygen therapy than among those given conventional oxygen therapy. The intubation rate did not differ significantly between HFNC oxygen therapy and noninvasive ventilation." (pg E266) |

| Main Study Findings | Authors' Conclusion |
|---|---|
| Pneumothorax rate: RR = 1.15 (95% CI 0.42; 3.14); 1 study<br>-Higher incidence of ventilator induced lung injury in NIV group, no difference in pneumothorax (8 patients in NHF group and 7 in NIV group) | |
| Zhu, 2017[14] | |
| **Escalation of respiratory support**<br>-NHF vs COT: RR = 0.68 (95% CI 0.37;1.27; *P* = 0.23)<br>-NHF > 24 hours vs COT (2 studies):<br>RR = 0.71 (95% CI, 0.53;0.97; *P* = 0.03)<br>-NHF < 24 hours vs COT (2 studies):<br>RR = 0.67; (95% CI 0.08;5.55; *P* = 0.71)<br>**Intubation rate**<br>-NHF vs COT: RR = 0.74 (95% CI 0.55;1.00; *P* = 0.05)<br>-NHF > 24 hours vs COT (2 studies):<br>RR = 0.71 (95% CI 0.53;0.97; *P* = 0.03)<br>-NHF < 24 hours vs COT (2 studies):<br>RR = 1.24 (95% CI 0.31;4.93; *P* = 0.76)<br>**Mortality**<br>-NHF vs COT (2 studies; $I^2$=78%; p = 0.03):<br>RR=0.82 (95% CI 0.36;1.88; *P* = 0.64)<br>**Complications**<br>-Studies did not report sufficiently | "The overall estimates of this meta-analysis showed that there were no significant differences between the HFNC and COT groups in the rates of escalation of respiratory support,… intubation,… mortality,… or ICU …in the treatment of ARF." (pg 7) |
| Mayfield, 2014[17] | |
| **No studies identified.** | |

ARF=Acute Respiratory Failure; COT=Conventional Oxygen Therapy; $CO_2$=Carbon Dioxide ; FiO2=Fraction of Inspired Oxygen; HFNC=High flow Nasal Cannulae; ICU=Intensive Care Unit; MD = Mean Difference; NHF=Nasal High Flow; NIV=Non-invasive ventilation; NIPPV = Non-Invasive Positive Pressure Ventilation; $O_2$=Oxygen; OR=Odds Ratio; PICO = Population, Intervention, Comparator, Outcome; PaO2=Partial Pressure of Oxygen ; PICU=Pediatric Intensive Care Unit; RCT=Randomized Controlled Trial; RR=Risk Ratio; $SpO_2$ = Pulse Oximetry; VAS=Visual Analogue Scale; VNS=Visual Numeric Scale; 95% CI=95% Confidence Interval

## Table 9: Summary of Findings of Included Primary Clinical Studies

| Main Study Findings | Authors' Conclusion |
|---|---|
| Azoulay, 2018[2] | |
| **NHF vs COT**<br>-All-cause day-28 mortality:<br>MD = −0.5 (95% CI −7.3 to 6.3); HR= 0.98 (95% CI 0.77 to 1.24); *P* = .94<br>-Invasive mechanical ventilation:<br>MD = −5.1 (95% CI −12.3 to 2.0);<br>HR= 0.85 (95% CI 0.68 to 1.06); *P* =.17<br>-ICU-acquired infection:<br>MD = −0.6 (95% CI −4.6 to 4.1); HR= 1.01 (95% CI 0.96 to 1.06); *P* = .91<br>-ICU mortality:<br>MD = 0.3 (95% CI −6.3 to 6.8); RR=1.01 (95% CI 0.82 to 1.24); *P* =.64<br>-Hospital mortality:<br>MD = −0.5 (95% CI −7.5 to 6.4); RR= 0.99 (95% CI 0.84 to 1.17); *P* =.77<br>-ICU length of stay- median days (IQR):<br>MD = 0.6 (95% CI −1.0 to 2.2); *P* = .07<br>-Hospital- median days (IQR): MD = −2 (95% CI −7.3 to 3.3); *P* =.60 | "This RCT found no significant survival benefits with high flow oxygen therapy compared with standard oxygen therapy in immunocompromised patients with AHRF. Neither were significant differences found for intubation requirements, ICU-acquired infections, subjective dyspnea and comfort, or ICU length of stay." (pg 2104) |

| Main Study Findings | Authors' Conclusion |
|---|---|
| -No significant difference in comfort or dyspnea scores using visual analogue scales<br>**Complications**<br>-Intolerance resulting in discontinuation from NHF (n=12; 3%), of whom 3 died. | |
| Ballestero, 2018[22] | |
| **NHF vs COT**<br>-Improvement in pulmonary scare within first two hours: 16 [53%] vs 9 [28%]; *P* = .01; OR = 4.70 (95% CI, 1.23;17.89); *P* = .02<br>-No significant difference in changes to $SpO_2/FiO_2$, RR, HR, length of stay, the need for respiratory support or duration or need for additional therapy, or return visits within 72 hours<br>**Complications**<br>-PICU admission occurred in first 2 hours: 1 patient (12%) vs 6 controls (66%); *P* = .03 | "The present study demonstrates that HFNC oxygen therapy is effective and safe for the treatment of children who experience episodes of severe asthma while in the ED. Although HFNC therapy has not been found to be more effective in terms of reducing hospitalization, its beneficial effects during the first hours of treatment make it an option to consider in the early treatment of severe asthma attacks." (pg 208) |
| Ergul, 2018[23] | |
| **NHF vs diffuser mask**<br>-Presence of treatment failure (n/%): 0 (0) vs 7 (23.3); *P* = 0.01<br>-Length of ICU stay (days): 3 (2/3) vs 4 (3/5); *P* < 0.001<br>-Length of hospital stay (days): 4 (3/4) vs 5 (4/6); *P* < 0.001<br>-Time to weaning off oxygen (h): 56 (42/72) vs 96 (72/101); *P* < 0.001<br>-Mechanical ventilation requirement: 0 (0): vs 0 (0)<br>-Re-admitted to ICU:0 (0) vs 0 (0)<br>-Respiratory rate (baseline to 48 hours):<br>MD = − 33.11 ± 47.67 vs − 23.89 ± 27.07 (*P* =0.367)<br>-Heart rate (baseline to 48 hours):<br>MD = 30.90 ± 9.77 vs − 22.90 ± 7.78 (*P* = 0.005) | "In our study, the success rate in patients administered oxygen therapy for acute bronchiolitis was twofold higher in those treated with an HFNC than in those treating using a diffuser mask. We also found that HFNC use decreased the time to weaning off oxygen and length of ICU stay compared to use of a diffuser mask." (pg 1306) |
| Ramnarayan, 2018[20] | |
| **NHF vs CPAP**<br>-Intubation within 72 hours:<br>RR = 2.44 (95% CI 0.59; 10.12), RD = 22.1 (95% CI −8.7;52.9)<br>-Crossover or escalation within 72 h:<br>RR = 1.63 (95% CI 0.63;4.21), RD = 19.2 (95% CI −15.8;54.3))<br>-Length of PICU stay (days): MD= 0.7 (95% CI −3.5;5.0)<br>-Length of hospital stay (days): MD= −7.8 (95% CI −28.9;13.3)<br>-Length of invasive ventilation from first escalation (day):<br>MD = −0.3 (95% CI -3.6;3.0)<br>-Length of treatment (days): MD = −0.3 (95% CI −1.1;0.5)<br>-Ventilator-free days at day 28: MD = −4.0 (95% CI −10.3;2.4)<br>-PICU mortality:<br>RR = 1.63 (95% CI 0.17;15.99; RD = 4.8 (95% CI −16.9;26.5)<br>-Hospital mortality:<br>RR = 1.63 (95% CI 0.17;15.99); RD = 4.8 (95% CI −16.9;26.5)<br>**Complications**<br>One patient with abdominal distension and one with facial thermal injury in NHF group, one with aspiration in CPAP group | "In this multi-centre pilot RCT...both treatments were safe and, although not powered to test for significance, outcome data suggested that the rate of intubation and length of respiratory support were potentially important outcomes to consider in a future RCT." (pg 8) |
| Sitthikarnkha, 2018[24] | |
| **NHF vs COT**<br>-Treatment failure: OR = 0.15 (95% CI 0.03;0.66); *P* = 0.01<br>-Respiratory rate: *P* = 0.03, favouring NHF<br>-Clinical respiratory distress score at 240 minutes: *P* = 0.03, favouring NHF | "The study revealed a potential clinical advantage of using HFNC in management children hospitalized with respiratory distress compared with conventional respiratory therapy. Most children recruited for this study were diagnosed with pneumonia." (pg 15) |

| Main Study Findings | Authors' Conclusion |
|---|---|
| **Complications**<br>-Epistaxis (n=1/49 in NHF group at 36 hours) | |
| Makdee, 2017[21] | |
| **NHF vs COT**<br>-RR at 60 minutes (breaths/min): MD = -3.3 (95% CI 1.9 to 4.6)<br>-Change in respiratory rate from 30–60 min, breaths/min: MD= –0.2 (95% CI –1.1 to 0.7)<br>-Mean arterial pressure at 60 min, mm Hg: MD = –3.6 (95% CI –8.9 to 1.8)<br>-Pulse rate at 60 min, beats/min: MD = 1.3 (95% CI –5.5 to 8.1)<br>-Oxygen saturation at 60 min, %: MD = –0.5 (95% CI –1 to –0.02)<br>-Dyspnea score at 60 min (0–10): MD = 0.5 (95% CI –0.3 to 1.2)<br>-Comfort score (0–10): MD = –1.8 (95% CI –2.4 to –1.1)<br>-Emergency Department length of stay, h: MD = –0.9 (95% CI –2.1 to 0.2)<br>-Admission rate, No.: MD = 6.7 (95% CI –13.8 to 27.3)<br>-Hospital length of stay: MD = 0.1 (95% CI –0.9 to 2.3)<br>-Noninvasive ventilation within 24 h, No: MD = 3 (95% CI –3.1 to 9.2)<br>-Intubation within 24 h, No: MD = –1.6 (95% CI –4.7 to 1.5)<br>-Mortality in 7 days, No. : MD =–1.6 (95% CI –4.7 to 1.5)<br>**Complications**<br>Intubation (n=1/63 in NHF); Severe discomfort (n=1/63 in NHF) | "In this randomized trial of ED patients with cardiogenic pulmonary edema, we observed that 60-minute respiratory rate was significantly lower with high-flow nasal cannula than conventional oxygen therapy. Similarly, the lower respiratory rates at 15 and 30 minutes were lower with high-flow nasal cannula. We found that high-flow nasal cannula could deliver effective oxygenation and comfort with minimal complications or life-threatening adverse events" (pg 470) |
| Mauri, 2017[19] | |
| **COT vs NHF (mean +/- SD, or median +/- IQR)**<br>Difference in Pes, cm $H_2O$: 9.9 +/- 4.2 vs 8.0 +/- 3.4 , $P < 0.01$<br>PTP, cm $H_2O$ x s: 9.5 (5.7 to 12.1) vs 7.4 (4.1 to 9.4) , $P < 0.01$<br>PTPmin, cm $H_2O$ x s/min: 216.3 +/- 100.5 vs 154.8 +/- 84.8 , $P <0.001$<br>PL,ee, cm $H_2O$: 210.1 +/- 5.0 vs 27.5 +/- 5.2 , $P < 0.001$<br>PL,ei, cm $H_2O$: 23.6 +/- 4.9 vs 22.6 +/- 4.5, $P = 0.16$<br>DPL, cm $H_2O$: 5.7 +/- 3.4 vs 4.3+/- 2.9 , $P = 0.08$<br>RR, bpm: 24 (20 to 27) vs 22 (17 to 24) , $P < 0.01$<br>Set $FiO_2$: 0.60 (0.50 to 0.75) vs 0.60 (0.50 to 0.75) $P = 1.00$<br>$PaO_2$ , mm Hg: 72 (68 to 75) vs 98 (78 to 131) , $P < 0.001$<br>$PaO_2$ /set$FiO_2$ , mm Hg: 130 +/- 35 vs 184 +/- 53 , $P <0.001$<br>$PaCO_2$ , mm Hg: 40.7 +/- 5.7 vs 41.1 +/- 5.9, $P = 0.27$<br>pH: 7.45 +/-: 0.02 vs 7.44 +/- 0.03, $P = 0.23$<br>SBP, mm Hg: 141 +/- 25 vs 137 +/- 27 , $P < 0.05$<br>MAP, mm Hg :90 +/- 15 vs 88 +/- 16, $P = 0.11$<br>CVP, mm Hg: 4.6 +/- 5.2 vs 5.8 +/- 4.7 , $P < 0.05$<br>HR, bpm: 85 +/- 9 vs 84 +/- 9, $P = 0.44$ | "The present study shows that in patients with AHRF, HFNC improves several key physiologic parameters including oxygenation, inspiratory effort, MV, RR and lung volume, dynamic lung compliance, transpulmonary pressure, and homogeneity" (pg 1210) |

AHFR= Acute hypoxemic respiratory failure; CPAP = Continuous positive airway pressure; CVP = central venous pressure ; DPes = inspiratory esophageal pressure swing; DPL = driving transpulmonary pressure; ED = Emergency Department; EIT=Electrical Impedance Tomography; $FiO_2$=Fraction of Inspired Oxygen; HFNC=High Flow Nasal Cannulae; $H_2O$=water; HR=Hazard Ratio; IQR=Interquartile range; MAP = mean arterial pressure; MD=Mean Difference; NHF=Nasal High Flow; PICU=Pediatric Intensive Care Unit; PL,ei = dynamic end-inspiratory transpulmonary pressure; PL,ee = dynamic end-expiratory transpulmonary pressure; $PtCO_2$ =transcutaneous carbon dioxide tension; PTPmin = pressure time product per minute; ; PTP = pressure-time product per breath;RR=Risk Ratio; RD=Risk Difference; SBP = systolic arterial blood pressure; $SpO_2$= Pulse Oximetry;VTdep = tidal volume distending dependent regions; VTnon-dep = tidal volume distending nondependent regions; 95% CI=95% Confidence Interval;

## Table 10: Summary of Findings of Included Economic Evaluation

| Main Study Findings | Authors' Conclusion |
|---|---|
| Eaton Turner, 2017, UK[25] | |
| *Effectiveness outcome is averted intubations*<br>**NHF vs COT**<br>–£469; Dominant (Probability of being cost-saving 95.6%)<br>Device cost (per patient) £102 vs £0.43<br>Intubation cost (per patient) £720 vs £891<br>Event leading to intubation cost (per patient) £609 vs £743<br>Complication cost (per patient) £380 vs £646<br>**NHF vs NIV**<br>–£611; Dominant (Probability of being cost-saving 99.1%)<br>Device cost (per patient) £102 vs £67.20<br>Intubation cost (per patient) £720 vs £948<br>Event leading to intubation cost (per patient) £609 vs £790<br>Complication cost (per patient) £380 vs £617 | "NHF was found to dominate against standard oxygen and NIV when used in patients who had not previously been intubated" (pg 336) |

NHF=Nasal High Flow; NIV=Non-invasive ventilation; COT = Conventional Oxygen Therapy

# Appendix 5: Overlap between Included Systematic Reviews

## Table 11: Primary Study Overlap between Included Systematic Reviews

| Primary Study Citation | Systematic Review Citation | | | | | | |
|---|---|---|---|---|---|---|---|
| | Ou, 2017[11] | Sklar, 2018[4] | Ni, 2017[16] | Zhu, 2017[14] | Nedel, 2017[12] | Monro-Somerville, 2017[13] | Leisching, 2017[15] |
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**Correction**

Table 1: Selection Criteria and the Exclusion Criteria have been modified from the original report, published February 14, 2019, to clarify the eligible patient population and handling of studies with mixed populations.

In the original report, published February 14, 2019, the eligible population described in Table 1 was: “Pediatric (non-neonatal) or adult patients being treated in hospital with an airway exacerbation or hypoxemic respiratory failure needing respiratory support.”

Table 1 has been modified to add “non-premature” to the description of the pediatric population. The following statement was also added to the Exclusion Criteria section of the report: “Studies with mixed pediatric populations were excluded when results were not analyzed and presented separately for the population of interest to this report (i.e., non-neonatal and non-premature patients).”