

Appendix 1: Summary of Studies

Table S1: Physiology and mechanisms

Table S1 summarises physiological and mechanistic studies relevant to HFNT. These studies support plausible mechanisms including heated humidification, mucociliary preservation, anatomical dead-space washout, more reliable FiO₂ delivery, low-level flow-dependent positive airway pressure, improved lung mechanics and reduced work of breathing. Most studies are bench, healthy-volunteer or small physiological crossover studies; therefore, they should be interpreted as mechanistic support rather than direct evidence of improved mortality, intubation avoidance or length of stay.

Mechanism / physiological domain	Study	Study type and population/model	Intervention / exposure	Outcomes measured	Key findings
Airway humidification and mucociliary function	Williams et al., 1996	Narrative/physiological review of airway mucosal function	Inspired gas humidity and temperature	Airway mucosal function, secretion properties, mucociliary performance	Synthesised evidence that inadequate humidification and suboptimal inspired gas temperature impair airway mucosal function.
Airway humidification and mucociliary function	Kilgour et al., 2004	Controlled laboratory study; in vitro ovine tracheal model	Reduction in inspired air temperature from 37°C to lower temperatures within the clinical range, at 100% relative humidity	Ciliary beat frequency and mucus transport velocity	Mucociliary function deteriorated as inspired gas temperature decreased within the clinical range.
Mucociliary clearance	Hasani et al., 2008	Single-centre physiological study; 14 bronchiectasis patients recruited, 10 completed	Domiciliary humidification: high-flow saturated air at 37°C for 3 h/day for 7 days	Radioaerosol tracheobronchial mucociliary clearance using 99mTc-labelled particles	Warm humidification improved lung mucociliary clearance in bronchiectasis.
Anatomical dead-space washout	Möller et al., 2015	Experimental upper-airway model study	Nasal high flow across model upper airways	Clearance of tracer gas / anatomical dead-space washout	Nasal high flow cleared anatomical dead space in upper-airway models.
Dead-space washout and interface design	Tatkov et al., 2023	Bench/model physiological study	Symmetrical vs asymmetrical nasal high-flow interface	CO ₂ clearance from anatomical dead space; positive airway pressure	Asymmetrical nasal high flow improved CO ₂ clearance from anatomical dead space and increased positive airway pressure compared with symmetrical configuration.
Delivered FiO ₂ reliability and upper-airway pressure	Ritchie et al., 2011	Healthy-volunteer physiological study; n=10	Humidified nasal high-flow oxygen at 10–50 L/min with FiO ₂ 0.60	Delivered/ calculated FiO ₂ , expired gases, hypopharyngeal pressure	Calculated FiO ₂ approached the set FiO ₂ at flows above approximately 30 L/min during resting nasal breathing; airway pressure increased with flow.
Low-level positive airway pressure	Parke et al., 2011	Physiological study in adults scheduled for elective cardiac surgery; n=15	Nasal high-flow oxygen at 30, 40 and 50 L/min, mouth open and closed	Nasopharyngeal airway pressure	Mean nasopharyngeal pressure rose with increasing flow; pressures were higher with mouth closed. At 50 L/min with mouth closed, reported pressure was approximately 3.3 cmH ₂ O.
Very-high-flow pressure and lung impedance	Parke et al., 2015	Healthy-volunteer physiological study; n=15	Nasal high-flow therapy at 30–100 L/min	Nasopharyngeal airway pressure and end-expiratory lung impedance	Airway pressure and end-expiratory lung impedance increased linearly with flow; breathing frequency decreased.
Ventilation and CO ₂ clearance in COPD	Bräunlich et al., 2016	Physiological study in COPD patients; n=38	Nasal high flow up to 60 L/min	Ventilatory parameters and hypercapnia	Nasal high flow improved ventilation parameters in COPD and provided preliminary evidence of CO ₂ reduction.
Flow, prong–nares ratio and ventilation in COPD	Bräunlich and Wirtz, 2024	Interventional physiological study; 25 stable hypercapnic COPD patients	Nasal high flow at 20–50 L/min using different prong sizes	Mean airway pressure, tidal volume, respiratory rate, minute ventilation, pCO ₂	Increasing flow increased mean airway pressure and reduced pCO ₂ when flow increased from 20 to 40 L/min; prong size did not significantly alter measured respiratory parameters or pCO ₂ .
Work of breathing and lung mechanics in acute hypoxaemic respiratory failure	Mauri et al., 2017	Prospective randomised crossover physiological study; 15 ICU patients with acute hypoxaemic respiratory failure	HFNT at 40 L/min vs standard non-occlusive face mask at same FiO ₂	Oxygenation, respiratory rate, oesophageal pressure swings, pressure-time product, minute ventilation, end-expiratory lung volume, dynamic compliance, ventilation homogeneity	HFNT improved oxygenation, reduced respiratory rate, inspiratory effort and work of breathing, increased end-expiratory lung volume, and improved dynamic compliance/ventilation homogeneity.
Work of breathing in stable hypercapnic COPD	Pisani et al., 2017	Randomised physiological crossover study; 14 stable hypercapnic COPD patients	HFOT at different flow/mouth conditions vs NIV	Transdiaphragmatic pressure, breathing pattern, gas exchange	HFOT and NIV improved breathing pattern and reduced inspiratory effort, although NIV had greater ventilatory support effect.

Post-extubation COPD neuroventilatory drive and work of breathing	Di Mussi et al., 2018	Single-centre unblinded crossover study; 14 post-extubation COPD patients recovering from hypercapnic respiratory failure	HFNT alternated with conventional low-flow oxygen	Electrical diaphragmatic activity and transdiaphragmatic pressure–time product	HFNT significantly reduced neuroventilatory drive and work of breathing compared with conventional oxygen.
Mechanistic synthesis	Spoletini et al., 2015	Narrative review	Adult heated humidified high-flow nasal oxygen	Mechanisms of action and clinical implications	Described mechanisms including humidification, improved comfort, reduced entrainment of room air, upper-airway washout, more stable FiO ₂ delivery and low-level positive pressure.

Table S2: Acute hypoxaemic respiratory failure - mixed populations and major syntheses

This table summarises key primary trials, systematic reviews and guideline-level sources relevant to HFNT in mixed acute hypoxaemic respiratory failure. Overall, HFNT appears to reduce treatment failure or intubation compared with conventional oxygen therapy in selected patients, but a consistent mortality benefit has not been demonstrated. Compared with NIV/CPAP, HFNT may be better tolerated but may provide less positive pressure and less improvement in oxygenation in some patients. Findings should be interpreted alongside disease-specific evidence, clinical trajectory, patient tolerance and escalation suitability.

Study / source	Design and setting	Population	Intervention and comparator	Main outcomes assessed	Key findings
Frat et al., 2015 (FLORALI trial)	Multicentre, open-label RCT in ICUs	310 adults with non-hypercapnic acute hypoxaemic respiratory failure; PaO ₂ /FIO ₂ ≤300 mmHg	HFNT vs conventional oxygen therapy vs NIV	Primary: intubation at day 28. Secondary: ventilator-free days, ICU mortality, 90-day mortality	Intubation did not differ significantly: 38% HFNT, 47% conventional oxygen, 50% NIV. Ventilator-free days were higher with HFNT. Ninety-day mortality favoured HFNT compared with both conventional oxygen and NIV.
Jones et al., 2016 (HOT-ER trial)	Single-centre RCT in emergency department	Adults with acute respiratory distress/hypoxaemia requiring oxygen support; n=303	Humidified HFNT vs standard oxygen therapy	Dyspnoea, respiratory rate, oxygenation, escalation/intubation and disposition outcomes	Demonstrated feasibility of ED HFNT and improvements in respiratory parameters/symptoms, but was not powered for definitive clinical outcomes.
Bell et al., 2015	RCT in emergency department	Adults presenting with acute hypoxaemic respiratory failure; n=100	HFNT vs standard oxygen therapy	Respiratory parameters, treatment escalation, tolerability	Small trial contributing to the broader evidence base comparing HFNT with conventional oxygen in acute hypoxaemia.
Rittayamai et al., 2015	Prospective randomised study in emergency department	Adults with acute dyspnoea and hypoxaemia; n=40	HFNT vs conventional oxygen therapy	Dyspnoea, respiratory rate, oxygenation, escalation	Suggested short-term symptomatic and physiological benefit of HFNT compared with conventional oxygen.
Rochwerg et al., 2019	Systematic review and meta-analysis of RCTs	Adults with acute hypoxaemic respiratory failure receiving HFNT or conventional O ₂ therapy; 9 RCTs; n=2093	HFNT vs conventional oxygen therapy	Mortality, intubation, escalation/treatment failure, ICU/hospital outcomes	Concluded that HFNT probably reduces intubation compared with conventional oxygen therapy, with no clear mortality effect.
Ferreyro et al., 2020	Systematic review and network meta-analysis	Adults with acute hypoxaemic respiratory failure; 25 RCTs; n=3804	Conventional oxygen, HFNT, NIV/CPAP and other non-invasive oxygenation strategies	Primary: all-cause mortality. Secondary: intubation and other outcomes	Network meta-analysis found no clear mortality superiority for HFNT; helped contextualise HFNT relative to NIV/CPAP and conventional oxygen.
Lewis et al., 2021 (Cochrane review)	Cochrane systematic review of RCTs	Adults in ICU requiring respiratory support; included acute respiratory failure and post-extubation populations; 31 studies; n=5136	HFNT vs standard oxygen; HFNT vs NIV/NIPPV	Treatment failure, mortality, ICU length of stay, pneumonia, oxygenation, comfort, adverse effects	HFNT may reduce treatment failure compared with standard oxygen, but probably makes little or no difference to mortality. Compared with NIV/NIPPV, HFNT showed no clear difference in treatment failure or mortality; oxygenation may be better with NIV/NIPPV.
Oczkowski et al., 2022 (ERS clinical practice guideline)	Evidence-based clinical practice guideline using GRADE	Adults with acute respiratory failure	HFNT considered alongside conventional oxygen therapy and NIV	Guideline recommendations across acute respiratory failure scenarios	ERS guideline provides evidence-based recommendations for HFNC/HFNT in adult acute respiratory failure and is directly relevant to national-guidance framing.
Frat et al., 2026 (SOHO trial)	Large multicentre open-label RCT in French ICUs	Adults with acute hypoxaemic respiratory failure; broad mixed population, commonly pneumonia/viral pneumonia; n=1116	HFNT vs standard oxygen therapy	Primary: 28-day mortality. Secondary: intubation, comfort/dyspnoea, respiratory rate, ventilator-free days, ICU/hospital outcomes	Reported no reduction in 28-day mortality with HFNT compared with standard oxygen; secondary reporting suggests lower intubation and better comfort with HFNT.
RENOVATE Investigators, 2025	Multicentre, adaptive, open-label, non-inferiority RCT across 33 Brazilian hospitals	1766 adults with acute respiratory failure across five groups, including non-immunocompromised hypoxaemic ARF, immunocompromised hypoxaemic ARF, COPD with respiratory acidosis, ACPE and hypoxaemic COVID-19	HFNT vs NIV	Primary: endotracheal intubation or death within 7 days	HFNT met prespecified non-inferiority criteria versus NIV for intubation or death within 7 days in 4 of 5 groups, including non-immunocompromised hypoxaemic ARF; immunocompromised hypoxaemic ARF was stopped for futility.

Table S3: Acute hypoxaemic respiratory failure - condition-specific evidence

Table S3 summarises condition-specific evidence for HFNT in acute hypoxaemic respiratory failure. Evidence is strongest in COVID-19, immunocompromised patients and cardiogenic pulmonary oedema, where randomised trials and systematic reviews are available. Evidence is substantially weaker for ILD, asthma, pulmonary embolism and bronchiectasis, where studies are generally small, observational, physiological or feasibility-focused. Clinical practice points should therefore distinguish between evidence supporting reduced escalation/intubation and evidence supporting symptom relief, comfort or physiological improvement.

Condition / clinical context	Study / source	Design and setting	Population	Intervention and comparator	Main outcomes assessed	Key findings
COVID-19 pneumonia	Ospina-Tascón et al., 2021 (HiFlo-COVID)	Multicentre open-label RCT	220 adults with severe COVID-19	HFNT vs conventional oxygen therapy	Invasive mechanical ventilation and time to clinical recovery	HFNT significantly decreased need for mechanical ventilation and time to clinical recovery compared with conventional oxygen therapy.
COVID-19 pneumonia	Grieco et al., 2021 (HENIVOT)	Multicentre RCT in 4 Italian ICUs	109 patients with COVID-19 and moderate-severe hypoxaemic respiratory failure	Helmet NIV vs HFNT	Days free of respiratory support at 28 days; intubation; mortality	No significant difference in days free of respiratory support; helmet NIV reduced intubation compared with HFNT, with no mortality difference.
COVID-19 pneumonia	Perkins et al., 2022 (RECOVERY-RS)	UK multicentre adaptive open-label RCT	1273 hospitalised adults with COVID-19 acute hypoxaemic respiratory failure	CPAP, HFNT or conventional oxygen therapy	Composite of tracheal intubation or mortality within 30 days	CPAP reduced the composite outcome compared with conventional oxygen therapy; HFNT did not significantly reduce the composite compared with conventional oxygen therapy.
COVID-19 pneumonia	Boudma et al., 2022 (COVIDICUS)	Multicentre factorial RCT in French ICUs	546 ICU patients with severe COVID-19 AHRF; 333 additionally randomised to oxygen support strategy	Standard oxygen vs CPAP vs HFNT	Time to invasive mechanical ventilation requirement at day 28	Standard oxygen, CPAP and HFNT had no significant impact on 28-day risk of IMV requirement in the non-IMV oxygenation-strategy population.
COVID-19 pneumonia	Frat et al., 2022 (SOHO-COVID)	Multicentre open-label RCT in 34 French ICUs	711 patients with COVID-19 respiratory failure and $\text{PaO}_2:\text{FiO}_2 \leq 200$ mmHg	HFNT vs standard oxygen via non-rebreathing mask	Primary: 28-day mortality. Secondary: intubation, ventilator-free days, ICU/hospital outcomes	No significant reduction in 28-day mortality; intubation was lower with HFNT: 45% vs 53%.
COVID-19 pneumonia with mild hypoxaemia	Crimi et al., 2023 (COVID-HIGH)	Multicentre open-label RCT	364 patients with COVID-19 pneumonia and mild hypoxaemia	HFNT vs conventional oxygen therapy	Escalation to CPAP, NIV or invasive ventilation within 28 days	Escalation occurred in 30.3% with HFNT and 38.6% with COT; difference was not statistically significant.
COVID-19 pneumonia / ARF comparator evidence	RENOVATE Investigators, 2025	Multicentre adaptive non-inferiority RCT	Adults with ARF across five prespecified groups; n=1766 overall; COVID subgroup n=882	HFNT vs NIV	Endotracheal intubation or death within 7 days	HFNT met non-inferiority criteria versus NIV for intubation or death within 7 days in the hypoxaemic COVID-19 group.
Immuno-compromised patients	Azoulay et al., 2018 (HIGH trial)	Multicentre RCT in 32 French ICUs	776 critically ill immunocompromised adults with AHRF requiring ≥ 6 L/min oxygen	HFNT vs standard oxygen therapy	Primary: 28-day mortality. Secondary: intubation, respiratory variables, comfort, ICU/hospital outcomes	HFNT did not significantly reduce 28-day mortality compared with standard oxygen: 35.6% vs 36.1%.
Immuno-compromised patients	Coudroy et al., 2022 (FLORALI-IM)	Multicentre open-label RCT in ICUs	Critically ill immunocompromised patients with acute respiratory failure; n=299	HFNT alone vs HFNT alternating with NIV	28-day mortality and intubation	Trial was designed to test whether HFNT alone reduced mortality compared with alternating NIV; no clear mortality advantage was demonstrated.
Immuno-compromised patients	Cortegiani et al., 2019	Systematic review and meta-analysis	Immunocompromised ICU patients with acute respiratory failure; 8 studies; n=1433	HFNT vs conventional oxygen therapy and/or NIV	Mortality and intubation	Found no mortality reduction with HFNT vs oxygen in immunocompromised patients, but reported reduced intubation rate vs oxygen.
Interstitial lung disease (acute or end-stage respiratory failure)	Koyauchi et al., 2018	Retrospective single-centre study	Patients with ILD, hypoxaemic respiratory failure and do-not-intubate orders; n=84	HFNT, with comparison to prior/supportive strategies depending on study design	Tolerability, survival and symptom/oxygenation outcomes	Suggested HFNT was feasible and tolerated in ILD patients with DNI orders.

Interstitial lung disease (acute exacerbation of IPF)	Vianello et al., 2019	Retrospective cohort / before-after clinical pathway study	Patients with acute exacerbation of idiopathic pulmonary fibrosis; n=17	Treatment algorithm incorporating HFNT	Short-term outcomes, oxygenation and mortality	Suggested HFNT could be incorporated into management of AE-IPF, with lower-than-expected short-term mortality in that cohort.
Interstitial lung disease (synthesis)	Pagliaro et al., 2024	Systematic review and narrative synthesis	12 studies, 715 patients with ILD across acute, chronic and end-stage settings	HFNT vs NIV, conventional oxygen or usual care depending on study	Oxygenation, dyspnoea, respiratory rate, length of stay, mortality, comfort	HFNT appeared potentially useful in ILD-related respiratory failure, with possible comfort/tolerability advantages; evidence remained limited and heterogeneous.
Acute asthma	Raeisi et al., 2019	Randomised double-blind pilot study	Inpatients with asthma exacerbation; n=39	High-flow oxygenation vs comparator oxygen strategy	Safety, dyspnoea and physiological parameters	Suggested feasibility and safety signals for high-flow oxygenation in inpatient asthma, but evidence remains preliminary.
Acute asthma	Geng et al., 2020	RCT	Adults with severe bronchial asthma complicated by respiratory failure; n=38	HFNT vs conventional oxygen therapy	Physiological and clinical improvement parameters	Reported potential benefit of HFNT in severe asthma with respiratory failure.
Acute severe asthma	Ruangsomboon et al., 2021	Pilot RCT in emergency/acute care setting	Acute severe asthma patients; n=37	Nasal high-flow oxygen vs conventional oxygen therapy	Dyspnoea, respiratory rate, gas exchange and escalation outcomes	Suggested possible dyspnoea/physiological improvement, but not definitive effects on intubation, PaO ₂ , PaCO ₂ or length of stay.
Pulmonary embolism	Messika et al., 2017	Retrospective case series	17 ICU patients with severe pulmonary embolism managed with HFNT	HFNT as respiratory support	Oxygenation and respiratory-rate response	Reported improved oxygenation and respiratory rate after transition to HFNT.
Pulmonary embolism	Aksakal et al., 2021	Small comparative study	ICU patients with acute PE and hypoxaemic respiratory failure; n=58	HFNT vs conventional nasal cannula oxygen	Oxygenation and respiratory parameters	Reported improved oxygenation and respiratory rate with HFNT compared with conventional oxygen.
Cardiogenic pulmonary oedema / acute heart failure	Makdee et al., 2017	Open-label RCT in emergency department	Patients with cardiogenic pulmonary oedema; n=128	HFNT vs conventional oxygen therapy	Dyspnoea, respiratory rate, oxygenation and escalation outcomes	Provided RCT evidence that HFNT may improve early respiratory distress/physiology compared with conventional oxygen in cardiogenic pulmonary oedema.
Cardiogenic pulmonary oedema / acute heart failure	Yan et al., 2023	Systematic review and meta-analysis	16 studies, 1333 patients with acute heart failure	HFNT vs COT or NIV	Intubation rate, respiratory rate, heart rate, oxygenation, hospital stay and dyspnoea	Compared with COT, HFNT reduced intubation rate and improved respiratory/oxygenation parameters; no significant differences were found between HFNT and NIV for several outcomes.
Cardiogenic pulmonary oedema / acute heart failure	RENOVATE Investigators, 2025	Multicentre adaptive non-inferiority RCT	Adults with ARF, including acute cardiogenic pulmonary oedema stratum; ACPE subgroup n=272	HFNT vs NIV	Intubation or death within 7 days	HFNT met prespecified non-inferiority criteria versus NIV for intubation or death within 7 days in the acute cardiogenic pulmonary oedema group.
Bronchiectasis / COPD-bronchiectasis exacerbation	Crimi et al., 2020	Single-centre, single-arm prospective feasibility study	Patients with AECOPD and documented bronchiectasis; pH ≥ 7.35 ; persistent tachypnoea despite treatment; n=15	HFNT	Dyspnoea, respiratory rate, SpO ₂ , arterial blood gases, sputum production, ease of expectoration	HFNT was feasible and associated with improved dyspnoea, lower respiratory rate, improved gas exchange and increased mucus production.
Cystic fibrosis bronchiectasis physiology	Sklar et al., 2018	Randomised crossover physiological study	Adult patients with cystic fibrosis; n=15	HFNT vs NIV	Diaphragmatic work, respiratory rate, minute ventilation, gas exchange and dyspnoea	HFNT and NIV had similar effects on diaphragmatic work, with HFNT reducing respiratory rate and minute ventilation.

Table S4: Acute hypercapnic respiratory failure

Table S4 summarises evidence for HFNT in acute hypercapnic respiratory failure. In non-acidotic or compensated hypercapnia, HFNT may reduce treatment failure compared with conventional oxygen in selected COPD patients, although findings are inconsistent. In acidotic AHRF, particularly AECOPD with pH <7.35, NIV remains the established first-line ventilatory support. HFNT may be considered when NIV is not tolerated, during planned NIV breaks, or as a monitored bridge, but should not delay escalation to NIV or invasive ventilation where clinically indicated.

Clinical comparison / context	Study	Design and setting	Population	Intervention and comparator	Main outcomes assessed	Key findings
HFNT vs conventional oxygen therapy: compensated/mild hypercapnia	Li et al., 2020	Tri-centre prospective randomised controlled trial	320 patients with AECOPD and acute compensated hypercapnic respiratory failure; pH 7.35–7.45 and PaCO ₂ >45 mmHg	HFNT vs conventional oxygen therapy	Treatment failure, defined as escalation to NIV or invasive ventilation; PaCO ₂ ; respiratory rate	HFNT reduced treatment failure compared with conventional oxygen therapy: 10.0% vs 19.4%, p=0.026, and improved PaCO ₂ /respiratory rate at 24 h.
HFNT vs conventional oxygen therapy: mild hypercapnia	Xia et al., 2022	Multicentre RCT across 16 tertiary hospitals in China	330 analysed patients with AECOPD and mild hypercapnia; pH ≥7.35 and PaCO ₂ >45 mmHg	HFNT vs conventional oxygen therapy	Primary: criteria for intubation during hospitalisation; secondary: treatment failure, length of stay, cost, mortality, 90-day readmission	Intubation criteria were met in 4/158 HFNT patients vs 1/172 COT patients, p=0.198; HFNT did not significantly reduce intubation in mild hypercapnic AECOPD.
HFNT vs conventional oxygen therapy: physiological effect	Pilcher et al., 2017	Randomised crossover physiological trial	24 patients with COPD exacerbations	Titrated oxygen via nasal high-flow cannula vs conventional oxygen delivery	Transcutaneous CO ₂ , respiratory rate, oxygen saturation and short-term physiological response	Demonstrated transient physiological effects on CO ₂ with nasal high-flow oxygen, without establishing hard clinical outcome benefit.
HFNT as rescue/alternative when NIV not tolerated	Yuste et al., 2019	Prospective observational ICU study	30 patients with moderate hypercapnic respiratory failure who could not tolerate or had contraindications to NIV; mixed causes including COPD exacerbation, cardiogenic pulmonary oedema, postoperative/post-extubation respiratory failure	HFNT without immediate NIV comparator	SpO ₂ 88-92%, respiratory rate, pH normalisation, need for ventilatory support	pH improved from 7.28 to 7.37 over 24 h; non-response occurred in 4/30 patients, including 3 requiring intubation.
HFNT vs NIV: acute acidotic/moderate AECOPD	Cortegiani et al., 2020	Multicentre non-inferiority RCT	Patients with AECOPD and mild-to-moderate acute hypercapnic respiratory failure; n=79 analysed	HFNT vs NIV as initial ventilatory strategy	PaCO ₂ reduction at 2 h, treatment failure/crossover, clinical outcomes	Short-term PaCO ₂ reduction was not significantly different, but a substantial proportion of HFNT patients crossed over to NIV.
HFNT vs NIV: acute-moderate hypercapnic AECOPD	Tan et al., 2024	Randomised open-label non-inferiority trial	225 patients with AECOPD and acute-moderate hypercapnic respiratory failure; pH 7.25-7.35 and PaCO ₂ ≥50 mmHg	HFNT vs NIV	Treatment failure and intubation	Treatment failure was higher with HFNT than NIV: 25.7% vs 14.3%, p=0.033; intubation was also higher with HFNT, 14.2% vs 5.4%.
HFNT vs NIV: mild-to-moderate hypercapnic AECOPD	Pantazopoulos et al., 2024	Multicentre randomised non-inferiority trial	105 patients with AECOPD and mild-to-moderate hypercapnic respiratory failure	Nasal high flow vs NIV	Treatment failure, physiological response and tolerance	Failure rates were not significantly different, but the study was underpowered; comfort/tolerance may favour nasal high flow.
HFNT vs NIV: acute hypercapnic respiratory failure, ED	Papachatzakis et al., 2020	Randomised clinical trial	40 ED patients with hypercapnic respiratory failure; PaCO ₂ ≥45 mmHg	HFNT vs NIV	PaCO ₂ , respiratory rate, mortality, organ failure, length of stay	Small trial reporting broadly similar clinical outcomes, with some physiological advantages reported for HFNT in PaCO ₂ /respiratory rate.
HFNT vs NIV: acute-moderate hypercapnic respiratory failure	Lee et al., 2018	Prospective observational study	92 patients with severe AECOPD and moderate hypercapnic acute respiratory failure; 44 HFNT vs 44 NIV	HFNT vs NIV	Intubation rate, 30-day mortality, blood gases	Intubation rate and 30-day mortality were not significantly different between HFNT and NIV; 30-day intubation 25.0% vs 27.3%, mortality 15.9% vs 18.2%.
HFNT vs NIV: high-velocity nasal insufflation	Doshi et al., 2018	Randomised controlled trial in ED	204 patients with undifferentiated respiratory failure requiring ventilatory support	High-velocity nasal insufflation vs NIPPV	Treatment failure/intubation and clinical outcomes	High-velocity nasal insufflation was non-inferior to NIPPV in the overall ED respiratory failure population.
HFNT at different flows vs NIV	Haciosman et al., 2025	Prospective randomised single-blind study	n=137; HFNC-30 n=44, HFNC-50 n=46, NIV n=47	HFNT at two flow rates vs NIV	Intubation, 28-day mortality and physiological outcomes	HFNC at 30 or 50 L/min produced short-term blood gas improvements that were comparable to NIV

HFNT vs NIV: small RCTs	Cong et al., 2019	RCT	AECOPD / type II respiratory failure; n=168; HFNC n=84, NIPPV n=84	HFNC vs NIV	Mortality, intubation, respiratory-support duration, ICU/hospital stay	No major ABG difference between both groups, better comfort/complications with HFNC
HFNT vs NIV: small RCTs	Wang et al., 2023	Retrospective propensity-matched study	AECOPD / type II respiratory failure; n=88	HFNT vs NIPPV/NPPV	Mortality, intubation, respiratory-support duration, ICU/hospital stay	Mortality did not differ after propensity matching, but treatment failure was higher with HFNC than NIV; patients failing HFNC and rescued with NIV had similar outcomes to those initially treated with NIV.
HFNT during NIV breaks	Spoletini et al., 2018	Pilot randomised controlled trial	Patients with acute respiratory failure receiving NIV; n=47	HFNT vs standard oxygen during breaks from NIV	Comfort, respiratory parameters, tolerance and complications	HFNT improved comfort-related outcomes during NIV breaks, but the study was not powered for mortality or intubation.
HFNT after NIV interruption	Longhini et al., 2019	Physiological crossover trial	Hypercapnic patients recovering after NIV; n=30	HFNT vs conventional oxygen after NIV interruption	Gas exchange and physiological stability	HFNT maintained physiological stability after NIV interruption without clear deterioration compared with oxygen.
Systematic review: HFNT vs NIV in AHRF	Ovtcharenko et al., 2022	Systematic review and meta-analysis of randomised trials	8 RCTs, 528 adults with acute hypercapnic respiratory failure, pH <7.35 or PaCO ₂ >45 mmHg	HFNT vs NIV	Mortality, intubation, length of stay, PaCO ₂ , PaO ₂ , respiratory rate, comfort and dyspnoea	Meta-analysis found uncertain differences between HFNT and NIV across several outcomes, but NIV remained the established first-line intervention.
Systematic review: HFNT vs conventional oxygen in hypercapnic COPD	Zhong et al., 2025	Systematic review and meta-analysis	9 RCTs, n=786	HFNC vs NIV in AECOPD	Treatment failure, gas exchange, respiratory rate, dyspnoea and adverse outcomes	No significant difference in mortality or intubation; HFNC reduced treatment intolerance but showed a non-significant trend toward higher treatment failure.

Table S5: Domiciliary HFNT in chronic respiratory failure

Table S5 summarises evidence for domiciliary or ambulatory HFNT in chronic respiratory failure. Evidence is strongest in COPD, particularly as an adjunct to LTOT in chronic hypoxaemic or stable hypercapnic disease, where randomised trial data suggest reductions in exacerbations and improvements in symptoms or health-related quality of life. Evidence in bronchiectasis is promising but largely observational. Evidence in ILD is mainly limited to small exercise-based crossover studies rather than long-term domiciliary outcomes. HFNT should not be presented as a replacement for NIV in established chronic hypercapnic ventilatory failure, and evidence in non-COPD chronic hypercapnic respiratory failure remains insufficient.

Clinical context	Study	Design and setting	Population	Intervention and comparator	Main outcomes assessed	Key findings
COPD with chronic hypoxaemic respiratory failure receiving LTOT	Storgaard et al., 2018	Randomised controlled trial; domiciliary setting	200 patients with COPD and chronic hypoxaemic respiratory failure receiving long-term oxygen therapy	Oxygen-enriched domiciliary HFNT plus usual care/LTOT vs usual care/LTOT alone	Exacerbations, hospital admissions, mMRC dyspnoea, SGRQ, FEV ₁ , 6MWT, PaCO ₂	Long-term HFNT reduced exacerbation frequency and improved dyspnoea, health-related quality of life and exercise capacity.
COPD with chronic hypoxaemic respiratory failure receiving LTOT	Sørensen et al., 2021	Health economic analysis based on domiciliary HFNT trial data	COPD patients with chronic respiratory failure receiving domiciliary HFNT; based on Storgaard n=200 trial	Domiciliary HFNT plus usual care vs usual care	Costs, quality-adjusted life years, incremental cost-effectiveness ratio	Suggested domiciliary HFNT may be cost-effective in COPD at commonly used willingness-to-pay thresholds.
Stable hypercapnic COPD receiving LTOT	Nagata et al., 2018	Multicentre randomised crossover trial; domiciliary setting	Stable hypercapnic COPD patients; n=32	Domiciliary HFNT plus LTOT vs LTOT alone	Dyspnoea, health-related quality of life, daytime/nocturnal PaCO ₂ and physiological variables	Six weeks of domiciliary HFNT plus LTOT improved dyspnoea and HRQoL and reduced daytime/nocturnal PaCO ₂ compared with LTOT alone.
Stable hypercapnic COPD receiving LTOT	Nagata et al., 2022	Multicentre randomised clinical trial; domiciliary setting	104 patients aged ≥40 years with GOLD stage 2-4 COPD, daytime hypercapnia, and LTOT use ≥16 h/day for ≥1 month	HFNT plus LTOT vs LTOT alone	Primary: moderate/severe exacerbation rate. Secondary: ABGs, SpO ₂ , pulmonary function, HRQoL and 6MWT	Home HFNT significantly reduced moderate/severe exacerbation rate in stable hypercapnic COPD receiving LTOT.
Stable chronic hypercapnic COPD: HFNT vs NIV	Bräunlich et al., 2019	Randomised controlled crossover trial	COPD patients with stable chronic hypercapnia; n=102	Nasal high flow vs non-invasive ventilation	PaCO ₂ reduction and tolerability	HFNT reduced PaCO ₂ , but NIV generally remains the established ventilatory support for chronic hypercapnic respiratory failure.
Stable chronic hypercapnic COPD: preliminary comparison with NIV	Bräunlich et al., 2015	Preliminary crossover study	11 stable hypercapnic COPD patients	Nasal high flow for 6 weeks followed by NIV for 6 weeks	pCO ₂ and tolerability	Nasal high flow reduced resting pCO ₂ ; no clear difference in pCO ₂ was observed between nasal high flow and NIV in this small preliminary study.
Chronic hypercapnic COPD / chronic respiratory failure: HFNT vs NIV	McKinstry et al., 2019	Randomised controlled crossover trial	COPD patients with chronic respiratory failure; n=24	Nasal high-flow therapy vs non-invasive ventilation	Physiological and patient-reported outcomes	Provides comparative evidence between home nasal high-flow therapy and NIV in chronic respiratory failure.
Home HFNT for chronic hypercapnic COPD	Pitre et al., 2023	Systematic review and meta-analysis	COPD patients with chronic hypercapnic respiratory failure receiving home HFNT; 4 RCTs; n=440	Home HFNT vs control/usual care or other respiratory support	HRQoL, gas exchange, exacerbations and clinical outcomes	Synthesised evidence suggests possible HRQoL benefit and physiological effects, but certainty remains limited.
COPD during exercise / pulmonary rehabilitation	Cirio et al., 2016	Physiological exercise study	Severe COPD patients with ventilatory limitation; n=12	Heated humidified high-flow gases during high-intensity constant-load exercise vs comparator oxygen condition	Exercise tolerance, oxygen saturation, dyspnoea, leg fatigue	HFNT improved oxygenation during constant-load exercise and reduced dyspnoea/leg fatigue compared with comparator conditions.
COPD during exercise / pulmonary rehabilitation	Prieur et al., 2022	Systematic review and meta-analysis of randomised trials	COPD patients receiving nasal high-flow therapy during exercise or exercise training; 8 studies; n=227	Nasal high-flow therapy vs usual oxygen/sham/comparator or during exercise	Functional exercise capacity, dyspnoea, HRQoL	Evidence across trials was heterogeneous and did not consistently demonstrate clinically meaningful improvements across all outcomes.
Bronchiectasis and chronic airway disease	Rea et al., 2010	Prospective open-label randomised controlled trial	108 patients with chronic airway disease, including COPD and bronchiectasis	Long-term humidification therapy vs usual care	Exacerbation days, time to first exacerbation, lung function, QoL, airway inflammation	Long-term humidification reduced exacerbation days, increased time to first exacerbation, and improved lung function/QoL.

Bronchiectasis	Crimi et al., 2022	Retrospective bicentric case-control study	20 bronchiectasis patients receiving home HFNT matched with 20 controls on optimised therapy	Long-term domiciliary HFNT vs optimised medical treatment alone	Exacerbations, hospitalisations, mucus features, symptoms, pulmonary function	Home HFNT was associated with significant reductions in exacerbations and hospitalisations and modest improvements in lung function.
Bronchiectasis	Simioli et al., 2023	Single-centre crossover/observational study	Adults with primary or secondary bronchiectasis and frequent exacerbations/hospitalisations; n=78	Long-term HFNT add-on therapy compared with prior/usual care period	Exacerbation rate, dyspnoea, tolerability, lung function	HFNT was well tolerated and associated with improved dyspnoea and reduced exacerbation rate, without significant change in lung function.
Bronchiectasis with hypercapnia	Yang et al., 2024	Retrospective observational study	70 bronchiectasis patients with hypercapnia receiving HFNT	HFNT as initial respiratory support	PaCO ₂ reduction, treatment failure and predictors of failure	HFNT reduced PaCO ₂ within 24 h; higher APACHE II score predicted treatment failure.
Chronic respiratory disease / home HFNT	Jácome et al., 2024	Systematic review	701 patients receiving long-term home HFNT for ≥4 weeks across chronic respiratory diseases	Home HFNT vs usual care or other home respiratory therapies	Dyspnoea, exacerbations, hospitalisations, SpO ₂ , comfort, HRQoL, PaCO ₂ , adherence and safety	Home HFNT appeared associated with reduced exacerbations, improved quality of life, good adherence and acceptable safety, but study quality varied.
Fibrotic ILD during exercise	Suzuki et al., 2020	Proof-of-concept randomised crossover trial	Patients with fibrotic interstitial lung disease; n=10	HFNT oxygen therapy vs comparator oxygen strategy during exercise	Exercise capacity and physiological response	Evaluated whether HFNT improves exercise capacity in fibrotic ILD; provides proof-of-concept support.
Idiopathic pulmonary fibrosis during exercise	Harada et al., 2022	Randomised crossover trial	Patients with idiopathic pulmonary fibrosis; n=24	HFNT oxygen therapy vs conventional oxygen strategy during exercise	Exercise tolerance and oxygenation	HFNT improved exercise tolerance in IPF in a controlled crossover setting.
Advanced obstructive airway disease during exercise	Chatila et al., 2004	Exercise physiology study	Patients with advanced obstructive airways disease; n=10	High-flow vs low-flow oxygen during exercise	Exercise performance, dyspnoea and oxygenation	High-flow oxygen improved exercise-related physiological outcomes compared with low-flow oxygen.

Table S6: Secretion management and airway clearance

Table S6 summarises evidence relevant to HFNT for secretion management and airway clearance. The evidence base is mechanistically plausible but clinically limited. Human physiological studies suggest that heated humidification can improve mucociliary clearance, and small observational or feasibility studies in COPD and bronchiectasis report improved sputum expectoration, mucus-related symptoms, exacerbation frequency or mucus plugging. However, there are no robust multicentre randomised trials specifically powered for secretion outcomes. HFNT should therefore be considered an adjunct to established airway clearance strategies rather than a stand-alone mucus-clearance therapy.

Clinical context	Study	Design and setting	Population	Intervention and comparator	Secretion / airway-clearance outcomes assessed	Key findings
Mechanistic humidification and mucociliary clearance	Williams et al., 1996	Physiological review / experimental synthesis	Airway mucosal physiology	Variation in inspired gas humidity and temperature	Airway mucosal function, secretion viscosity, mucociliary transport	Inadequate humidification and suboptimal inspired gas temperature impair airway mucosal function and secretion handling.
Mechanistic humidification and mucociliary clearance	Kilgour et al., 2004	Laboratory physiological study	In vitro tracheal model	Inspired gas temperature/humidity manipulation	Ciliary beat frequency and mucus transport velocity	Mucociliary function deteriorated when inspired gas temperature fell below optimal physiological conditions.
Bronchiectasis: mucociliary clearance	Hasani et al., 2008	Single-centre physiological study	Bronchiectasis patients; n=14 recruited; n=10 completed	Domiciliary high-flow saturated humidified air at 37°C for 3 h/day for 7 days; before-after assessment	Radioaerosol tracheobronchial mucociliary clearance using 99mTc-labelled particles	Domiciliary humidification improved lung mucociliary clearance in bronchiectasis.
Chronic airway disease: exacerbations and airway inflammation	Rea et al., 2010	Prospective open-label randomised controlled trial	108 patients with chronic airway disease, including COPD and bronchiectasis	Long-term humidification therapy vs usual care over 12 months	Exacerbations, lung function, quality of life, exercise capacity and airway inflammation	Long-term humidification reduced exacerbation days, increased time to first exacerbation, and improved lung function and QoL.
Bronchiectasis: post-hoc analysis of long-term humidification therapy	Good et al., 2021	Post-hoc analysis of bronchiectasis participants from Rea et al.	Bronchiectasis subgroup; n=45	Long-term high-flow humidification/HFNT vs usual care	Exacerbation rate, quality of life and related clinical outcomes	Reported reduced exacerbation rate and improved quality of life in bronchiectasis. HFNT is associated with reduced exacerbation frequency and improved quality-of-life measures.
Acute exacerbation COPD with coexisting bronchiectasis	Crimi et al., 2020	Single-centre, single-arm prospective feasibility study	Patients with AECOPD and documented bronchiectasis; n=15	HFNT during acute exacerbation	Dyspnoea, respiratory rate, oxygenation, arterial blood gases, sputum production, ease of expectoration	HFNT was associated with improved dyspnoea, lower respiratory rate, improved gas exchange, increased mucus production and easier expectoration.
AECOPD recovery: home HFNT feasibility and airway clearance	D'Cruz et al., 2025	Single-centre mixed-methods feasibility RCT	Patients recovering from severe AECOPD; n=18 randomised	Home HFNT plus usual care vs usual care	Feasibility, symptoms, physiology, patient experience; airway clearance and breathlessness signals	Home HFNT after severe AECOPD was safe and acceptable, with potential improvements in airway clearance and breathlessness.
Bronchiectasis: long-term domiciliary HFNT	Crimi et al., 2022	Preliminary retrospective bicentric case-control study	Bronchiectasis outpatients on optimised medical therapy; HFNT cases n=20, matched controls n=20	Long-term domiciliary HFNT vs optimised medical treatment alone	Exacerbations, hospitalisations, mucus features, difficulty of expectoration, symptoms, lung function	HFNT was associated with reduced exacerbations and hospitalisations, slight lung function improvement, and assessment of mucus features/expectoration difficulty.
Bronchiectasis: long-term HFNT add-on therapy	Simioli et al., 2023	Single-centre retrospective/ crossover study	Adult primary and secondary bronchiectasis; n=78	Long-term HFNT as add-on therapy compared with usual care/previous period	Exacerbations, dyspnoea, lung function and tolerability	HFNT was well tolerated; dyspnoea improved and exacerbation rate decreased, without significant change in lung function.
Bronchiectasis: disease severity and adherence	Calabrese et al., 2024	Retrospective cohort study	Non-cystic fibrosis bronchiectasis patients receiving long-term HFNT; BSI ≥9 n=50, BSI <9 n=36	Home HFNT for 12 months	Annual exacerbation rate, dyspnoea, lung function, sputum microbiology; relationship with bronchiectasis severity and daily use	Long-term HFNT reduced annual exacerbation rate; effect appeared greater with higher bronchiectasis severity and greater daily use.

Bronchiectasis: mucus plugs	Crimi et al., 2025	Short report / observational imaging-focused study	Bronchiectasis patients treated with long-term HFNT; n=20	Long-term HFNT	CT mucus plug score	Patients with bronchiectasis treated with long-term HFNT showed significant improvement in mucus plug score.
Bronchiectasis with hypercapnia	Yang et al., 2024	Retrospective observational study	Bronchiectasis patients with hypercapnia; n=70	HFNT as initial respiratory support	PaCO ₂ response, treatment failure predictors; indirectly relevant to secretion burden	HFNT reduced PaCO ₂ within 24 h; higher APACHE II score predicted treatment failure.
Home HFNT across chronic respiratory disease	Jácome et al., 2024	Systematic review	701 patients receiving long-term HFNT for ≥4 weeks across chronic respiratory disease	Home HFNT vs usual care or other home respiratory therapies	Dyspnoea, exacerbations, hospitalisations, comfort, HRQoL, PaCO ₂ , adherence, safety	Long-term HFNT appeared to reduce exacerbations and improve quality of life, with good adherence and safety, although study quality varied.
Airway clearance standards: bronchiectasis	Hill et al., 2019 (BTS bronchiectasis guideline)	National clinical guideline	Adults with bronchiectasis	Physiotherapy-led airway clearance and bronchiectasis care pathways	Airway clearance recommendations	Airway clearance techniques are a core component of bronchiectasis management.
Airway clearance standards: bronchiectasis	Polverino et al., 2017 (ERS bronchiectasis guideline)	International clinical guideline	Adults with bronchiectasis	Evidence-based bronchiectasis management	Airway clearance and chronic management	Reinforces airway clearance as standard bronchiectasis care.
Airway clearance techniques	Herrero-Cortina et al., 2023 (ERS statement on airway clearance techniques)	ERS statement	Adults with bronchiectasis	Airway clearance techniques	Physiotherapy-led airway clearance, indications and implementation	Provides contemporary consensus/evidence synthesis for airway clearance techniques in bronchiectasis.
Airway clearance standards: cystic fibrosis	Flume et al., 2009 (CF pulmonary guideline)	Clinical practice guideline	Patients with cystic fibrosis	Airway clearance therapies	Airway clearance recommendations	Establishes that airway clearance therapies are standard in CF lung disease.

Table S7: Practical implementation, monitoring, community delivery and withdrawal/palliation guidance

Table S7 summarises implementation, governance and palliative-care sources relevant to HFNT delivery. These sources do not provide trial evidence of HFNT efficacy, but support safe service design, monitoring standards, escalation planning, community transfer arrangements and ethically grounded withdrawal processes. Recommendations in these areas are therefore based on safety principles, national guidance, audit findings and extrapolation from established respiratory support and palliative-care frameworks.

Topic	Source / evidence type	Relevant content	Key takeaways
HFNT as acute respiratory support requiring monitored care	BTS Respiratory Support National Audit 2023	Audit evidence and recommendations around delivery of acute respiratory support, including NIV, CPAP and HFNT, in respiratory support units or equivalent monitored areas.	Supports the practice point that acute HFNT should be delivered in RSU, HDU, critical care or equivalent monitored environments rather than unenhanced wards. The statement draft already cites this audit in relation to ward use, infrastructure and outcomes.
NEWS2-based acuity and monitoring	NEWS2 / Royal College of Physicians framework	NEWS2 ≥ 5 indicates increased risk and need for urgent clinical review and enhanced monitoring.	Supports framing HFNT patients as high-acuity patients requiring frequent physiological observations, senior review and escalation planning. The draft explicitly links HFNT acuity to NEWS2 monitoring expectations.
Oxygen prescribing and target saturations	BTS oxygen guideline	Provides oxygen target saturation ranges and principles for oxygen prescribing in adults.	Supports the statement's practical emphasis on prescribed oxygen targets, monitoring and avoiding uncontrolled oxygen in patients at risk of hypercapnia. The statement already cites the BTS oxygen guideline in the acute respiratory failure section.
Acute escalation planning	BTS/respiratory support governance principles and NIV practice standards	Non-invasive respiratory support requires treatment ceilings, escalation plans, staff competency and failure criteria.	Supports requiring a documented escalation plan before or at HFNT initiation, including suitability for NIV, invasive ventilation and ceiling of care. This is central to the practical acute HFNT section.
Oxygen infrastructure and transfer safety	NHS England patient safety alert: interruption of high-flow nasal oxygen during transfer	Highlights risk from interruption of HFNT during transfer and the need for safe transfer planning.	Supports the community/practical statement that patients dependent on HFNT require specialist transfer planning, handover, contingency oxygen arrangements and equipment familiarity. The draft cites this in the community transfer section.
Home oxygen and domiciliary respiratory support governance	BTS home oxygen guideline	Provides principles for home oxygen assessment, prescription, safety, follow-up and service delivery.	Supports the statement's domiciliary HFNT requirements: multidisciplinary oversight, backup plans, equipment servicing, power-failure planning and integration with home oxygen/community teams.
Community delivery and commissioning	Expert consensus / service-implementation principles	Home HFNT requires coordinated acute, community, specialist respiratory, home oxygen, ventilation and palliative care input where relevant.	Supports the statement's recommendation that community HFNT delivery should involve both acute and community teams, with clear responsibility for clinical oversight and device management.
Withdrawal of treatment and legal framework	GMC end-of-life guidance; Mental Capacity Act framework	Patients with capacity can refuse or discontinue medical treatment; best-interests processes apply when capacity is lacking; ADRT/LPA frameworks must be followed.	Supports the statement's distinction between withdrawal of HFNT as withdrawal of treatment, not assisted dying, and the need for documented capacity/best-interests decision-making.
Withdrawal of ventilatory/respiratory support	ICU/end-of-life consensus guidance, including Truog et al.	Provides principles for withdrawal of life-sustaining respiratory support, symptom control and multidisciplinary decision-making.	Supports extrapolation from NIV/ventilatory withdrawal literature to HFNT withdrawal, particularly around anticipatory prescribing, senior leadership and MDT communication.
Palliative management of breathlessness	Mahler et al.; Rocker et al.; Maddocks et al.	Established palliative approaches to dyspnoea, anxiety, non-pharmacological measures, opioids/anxiolytics where appropriate, and holistic support.	Supports the statement's recommendations for anticipatory symptom management, fan therapy, positioning, mouth care and specialist palliative care involvement.