Critical care 2

High-flow oxygen therapy and other inhaled therapies in intensive care units

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Summary

In this Series paper, we review the current evidence for the use of high-flow oxygen therapy, inhaled gases, and aerosols in the care of critically ill patients. The available evidence supports the use of high-flow nasal cannulae for selected patients with acute hypoxaemic respiratory failure. Heliox might prevent intubation or improve gas flow in mechanically ventilated patients with severe asthma. Additionally, it might improve the delivery of aerosolised bronchodilators in obstructive lung disease in general. Inhaled nitric oxide might improve outcomes in a subset of patients with postoperative pulmonary hypertension who had cardiac surgery; however, it has not been shown to provide long-term benefit in patients with acute respiratory distress syndrome (ARDS). Inhaled prostacyclins, similar to inhaled nitric oxide, are not recommended for routine use in patients with ARDS, but can be used to improve oxygenation in patients who are not adequately stabilised with traditional therapies. Aerosolised bronchodilators are useful in mechanically ventilated patients with asthma and chronic obstructive pulmonary disease, but are not recommended for those with ARDS. Use of aerosolised antibiotics for ventilator-associated pneumonia and ventilator-associated tracheobronchitis shows promise, but the delivered dose can be highly variable if proper attention is not paid to the delivery method.

Lancet 2016; 387: 1867–78

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See Series *Lancet Respir Med* 2016; **4:** 407–18

This is the second in a Series of three papers about critical care

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Introduction

Respiratory diseases account for a large portion of admissions to the intensive care unit. The lungs are unique both in their exposure to the outside environment and as a part of the cardiopulmonary circuit, exposed to the entirety of the body's circulation. Given these attributes, it is logical that inhaled therapies function as treatments for a range of conditions encountered in critical care. Various devices and drug formulations have been developed to specifically target the lung parenchyma, vasculature, and airways. In this Series paper, we discuss the current evidence regarding the use of inhaled therapies in critical care, including high-flow nasal cannulae (HFNC), heliox, nitric oxide, prostacyclins, bronchodilators and steroids, and antibiotics. We systematically searched the literature to provide the basis for this Series paper.

HFNC

The traditional nasal cannulae for oxygen administration is typically used at flows of 2–4 L/min. At these low flows, large dilution occurs with room air and thus the fraction of inspired oxygen (F_iO_2) is less than 0·4 L/min. Flows greater than 6 L/min can cause much discomfort when breathing in dry oxygen. Unheated bubble humidifiers can be used, but are inefficient and their efficiency decreases with increases in flow. Systems to deliver heated and humidified oxygen at flows as high as 60 L/min through a nasal cannula have become available in the past 10 years. The HFNC system consists of an air–oxygen blender, flow meter, heated humidifier, and nasal prongs, configured to provide a high airflow (figure 1).[1–3]

Due to the high gas flow (≤60 L/min) with an HFNC, little entrainment of room air can occur, allowing a precise F_iO_2 at high flows.[1–3] Additionally, the high flow flushes out expired gas from the upper airway, which increases the inspired oxygen concentration on the subsequent inhalation. Because the gas is warmed and humidified, it is more comfortable than standard oxygen therapy. Dyspnoea seems to be less often reported with

Search strategy and selection criteria

We searched PubMed for articles published in English between Dec 20, 2005, and Dec 17, 2015. We used the search terms "oxygen" in combination with "cannula" and "high flow"; "heliox" in combination with "humans" or "helium" in combination with "oxygen" and "humans"; "hypoxemia" in combination with "nitric oxide" and "humans"; "mechanical ventilation", "respiratory failure", or "hypoxemia" in combination with "epoprostenol", "prostacyclin", "veletri", or "iloprost", in combination with "aerosol", "nebulizer", or "inhaled"; "mechanical ventilation" or "positive pressure ventilation" in combination with "bronchodilator", "steroid", "corticosteroid", "beta agonist", or "anticholinergic" in combination with "aerosol", "nebulizer", or "inhaler"; "inhalation" or "inhaled" in combination with "anti-bacterial agents" or "antibiotics", in combination with "aerosol" or "nebulizer", in combination with "mechanical ventilation", "critical care", or "intensive care". We also searched the reference lists of articles identified by our search strategy and selected those we judged relevant. Additionally, we selected some references based on our previous knowledge of the subject. No exclusion criteria were used.

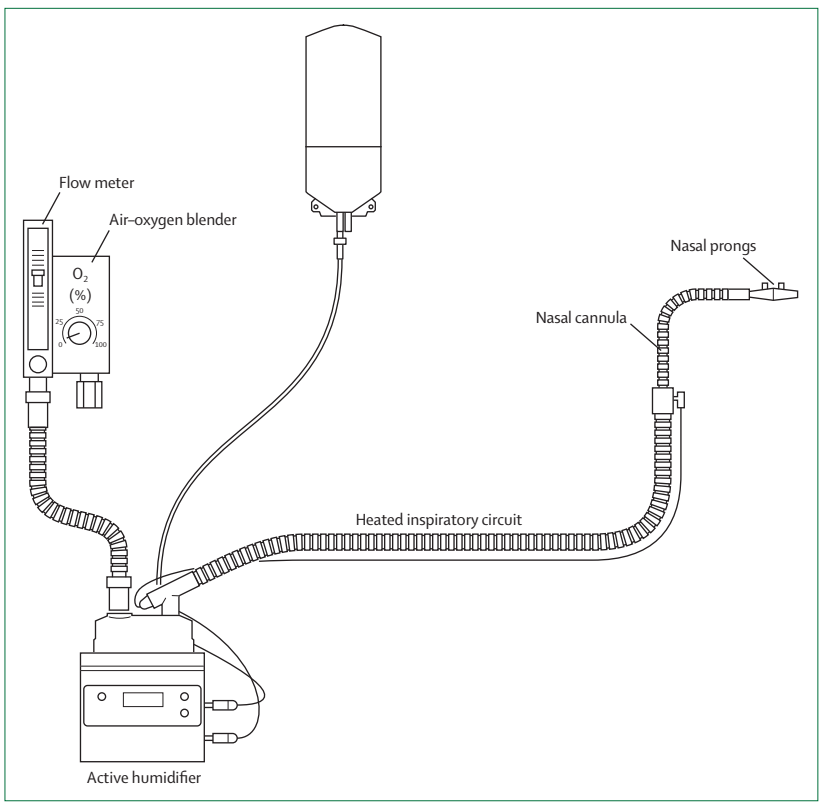

Figure 1: **Equipment to administer high-flow nasal cannulae**
Reproduced from Nishimura,[3] by permission of Daedalus Enterprises.

use of HFNC than with use of other devices. HFNC might also be more comfortable than a facemask, and removal of the device occurs less often with HFNC. This high-flow device might aid in airway clearance because the gas is fully warmed and humidified, but this theory has not yet been studied.

Flushing of the upper airway with HFNC reduces dead space.[4] This effect results in a reduced minute ventilation requirement[5] and is consistent with the common finding of a lower respiratory rate with HFNC than with other approaches. The high-gas flow reduces inspiratory resistance, possibly contributing to reduced severity of dyspnoea. The HFNC also impedes expiratory flow, which can produce distending pressure similar to continuous positive airway pressure. Parke and colleagues[6] reported that hypopharyngeal pressure increases by about 1 cm H_2O per 10 L/min flow with HFNC applied at 30–100 L/min, which is associated with an increase in lung volume.[7] However, the effect of continuous positive airway pressure is less with mouth open versus mouth closed.[8] Chanques and colleagues[9] measured tracheal pressure and found that HFNC provided a low level of positive pressure at 30 L/min or more with the mouth closed, but this effect was lost with an open mouth.

The most logical use for HFNC is to treat severe hypoxaemic respiratory failure that cannot be reversed by lower oxygen flows. Frat and colleagues[10] included 310 patients with acute hypoxaemic respiratory failure who were randomly assigned to receive HFNC, standard oxygen therapy by facemask, or non-invasive positive-pressure ventilation (NIV); in the NIV group, patients received HFNC if not using NIV. After 28 days, intubation was needed for 40 (38%) of 106 patients with HFNC, 44 (47%) of 94 patients with standard oxygen therapy, and 55 (50%) of 110 patients with NIV (p=0·18). The subgroup with a ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/F_iO_2) of 200 mm Hg or lower had a lower intubation rate with HFNC than with the other two methods (p=0·009).[10] The hazard ratio for death at 90 days was 2·01 (95% CI 1·01–3·99) with standard oxygen versus HFNC and 2·50 (1·31–4·78) with NIV versus HFNC.[10]

Jones and colleagues[11] randomly assigned 303 participants in the emergency department with hypoxaemic respiratory failure to receive HFNC or standard oxygen therapy. Less mechanical ventilation within 24 h of starting treatments was needed in the HFNC group than the standard oxygen therapy (5·5% *vs* 11·6%; p=0·053). In another emergency department study, Rittayamai and colleagues[12] randomly assigned 40 patients with acute dyspnoea and hypoxaemia to receive HFNC or conventional oxygen therapy for 1 h. No differences were reported in arterial oxygen saturation by pulse oximetry (SpO_2; p=0·13) or respiratory rate (p=0·82) between groups, but dyspnoea (p=0·01) and comfort (p=0·01) were lower for HFNC.

In a non-inferiority study, Stéphan and colleagues[13] randomly assigned 830 patients with hypoxaemic respiratory failure to receive HFNC (50 L/min with 50% oxygen) or NIV (pressure support 8 cm H_2O and positive end-expiratory pressure [PEEP] 4 cm H_2O) for at least 4 h per day. Unsuccessful treatment (21% for HFNC, 22% for NIV), intensive care unit mortality (6·8% for HFNC, 5·5% with NIV), dyspnoea, PaO_2/F_iO_2, respiratory rate, and comfort were similar for both treatments.[13] Skin breakdown was significantly more common in patients with NIV than in those with HFNC (10% *vs* 3%, p<0·001).[13] Thus, in this study,[13] outcomes were mostly similar for HFNC and NIV. Frat and colleagues[14] evaluated the clinical efficacy of HFNC alternating with NIV in hypoxaemic respiratory failure, showing HFNC was better tolerated than NIV and resulted in significant improvement in oxygenation and tachypnoea compared with standard oxygen therapy. HFNC seems to be more effective than standard oxygen therapy and NIV for hypoxaemic respiratory failure, regarding both major outcomes and comfort. More compelling evidence exists for the benefit of HFNC compared with standard oxygen therapy versus HFNC compared with NIV, in patients with hypoxaemia.

HFNC also seems to be efficacious in the postextubation setting. In a randomised crossover study, Rittayamai and colleagues[15] compared use of HFNC with non-rebreathing

masks in 17 patients after extubation. With HFNC, less dyspnoea (p=0·04), lower respiratory rate (p=0·009), and a lower heart rate (p=0·006) were reported; 88% of patients preferred HFNC to the non-rebreathing mask. Maggiore and colleagues[16] compared the use of an air entrainment mask with HFNC in 105 patients after extubation and who had PaO_2/F_iO_2 300 mm Hg or lower immediately before extubation. With HFNC, PaO_2/F_iO_2 was higher, discomfort associated with the interface and airway dryness was lower, fewer displacements of the interface were noted, and fewer desaturations were reported. Most importantly, fewer re-intubations were needed (4% *vs* 21%; p=0·01) or reduced need for any form of ventilator support in the HFNC group than in the mask group. In 2016, Hernandez and colleagues[17] reported that in extubated patients at low risk for re-intubation, use of HFNC compared with conventional oxygen therapy reduced the risk of re-intubation within 72 h.

HFNC can improve oxygenation during intubation. Miguel-Montanes and colleagues[18] did a before–after study in 101 patients with mild to moderate hypoxaemia who required intubation, comparing use of HFNC with a non-rebreathing mask. The median lowest SpO_2 during intubation was 94% with the non-rebreathing mask and 100% with HFNC (p<0·0001).[18] Vourc'h and colleagues[19] randomly assigned 124 patients with PaO_2/F_iO_2 of less than 300 mm Hg to receive HFNC (60 L/min) or high-flow face mask treatment for pre-oxygenation before intubation. The median lowest SpO_2 was 89·5% for the high-flow face mask and 91·5% for HFNC (p=0·44).[19] In Semler and colleagues' study,[20] 150 adults undergoing endotracheal intubation were randomly assigned to receive 15 L/min of 100% oxygen via HFNC (apnoeic oxygenation) or no supplemental oxygen during laryngoscopy (standard care). Median lowest arterial oxygen saturation was 92% with apnoeic oxygenation versus 90% with standard care.[20] The cannula remains in place with HFNC, which best explains this effect, whereas the oxygen delivery device is removed with other approaches.

Another potential use for HFNC is as a vehicle for delivery of inhaled aerosol therapy, although further study is needed to investigate this application.[21] Preclinical studies report strategies to improve delivery of these drugs during high flows, but these must be clinically validated.[22]

The available evidence supports the use of HFNC for selected patients with acute hypoxaemic respiratory failure (figure 2). It can also be used to prevent hypoxaemic respiratory failure, such as postextubation and during intubation. HFNC is initiated at a flow of 50 L/min, after which the flow is maintained and F_iO_2 is decreased, providing SpO_2 is more than 90%. Once HFNC is initiated, typically the F_iO_2 is decreased rather than the flow. If the F_iO_2 reaches 0·4, consideration can be given to a change to conventional oxygen therapy.

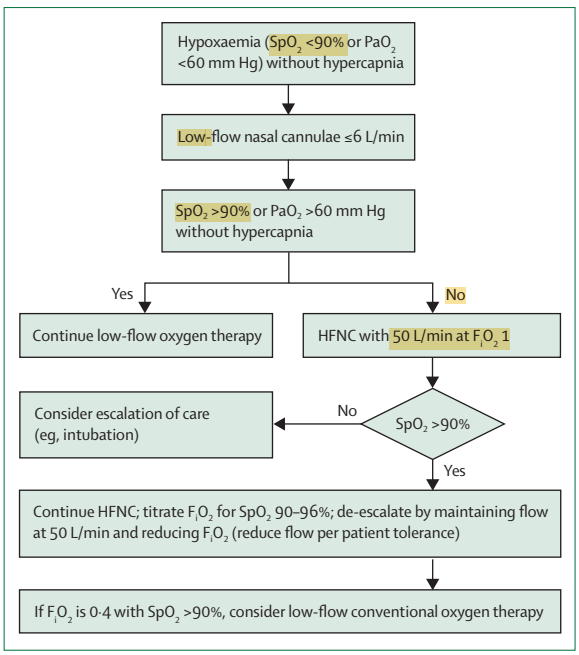

Figure 2: **Flow diagram of use of high-flow nasal cannulae for hypoxaemic acute respiratory failure**
SpO_2=arterial oxygen saturation by pulse oximetry. PaO_2=arterial oxygen partial pressure. HFNC=high-flow nasal cannulae. F_iO_2=fraction of inspired oxygen.

Although HFNC can improve hypoxaemia, comfort, and severity of dyspnoea, some patients will be intolerant of 50 L/min flow and a lower flow might be necessary for patient tolerance. HFNC might improve patient outcomes in those with hypoxaemic respiratory failure. Its use in other forms of respiratory failure, such as chronic obstructive lung disease (COPD) and acute cardiogenic respiratory failure, is yet to be determined. Unsuccessful use of HFNC might cause delayed intubation and worse clinical outcomes in patients with respiratory failure.[23]

Heliox

Helium is a non-toxic noble gas with a density of 0·18 g/m³, which is much lower than oxygen (1·43 g/m³) and nitrogen (1·25 g/m³).[24] Heliox is a mixture of helium and oxygen (usually in a helium:oxygen ratio of 80:20 or 70:30). This gas has been used for decades in the care of patients with various respiratory diseases, albeit with little evidence to guide its use. Its low density affords heliox a unique niche in the critical care setting, with potential applications for partial upper airway obstruction and obstructive lung diseases, such as asthma and COPD. Breathing in heliox might help to reduce the work of breathing and could be used to effectively deliver aerosolised drugs to the distal airways. Use of heliox is limited to patients with low F_iO_2 requirements, given the predominance of helium in the admixture. As the oxygen proportion increases (and hence helium decreases), gas density increases, thus restricting the potential benefit of heliox.

The low density of heliox facilitates the transition of turbulent to laminar flow by reducing the Reynolds number.[24] With reduction of turbulent flow, the pressure needed to generate the same total flow is reduced, thus decreasing the work of breathing. Intrinsic PEEP, hyperinflation, and partial pressure of carbon dioxide ($PaCO_2$) might be reduced. The reduction in $PaCO_2$ might be associated with increased alveolar ventilation or decreased carbon dioxide production due to lower work of breathing. The increased viscosity of heliox compared with nitrogen might increase resistance in the distal airways where flow is laminar (even in obstructive conditions), potentially providing an explanation for the equivocal evidence of benefit for heliox in conditions affecting the distal airways.[25]

Given the often emergent nature of partial upper airway obstruction, the use of heliox in this setting remains inadequately studied.[25] Heliox use might be considered for stabilisation of disease and to help decrease work of breathing, while serving as a bridge to definitive therapy (eg, bronchoscopy, surgery, radiation therapy, chemotherapy, or corticosteroids).

Emergency department studies[26] have shown the benefit of heliox in reducing rates of admissions to hospital for asthma exacerbations. A case series[27] of seven patients intubated with status asthmaticus showed rapid reductions in airway pressures and carbon dioxide retention with resolution of acidosis after initiating heliox.

A single centre study[28] of heliox versus placebo in 81 decompensated patients with COPD in the emergency department reported an impressive reduction in need for intubation (heliox 8% *vs* placebo 50%, p<0·01) and reduction in mortality (heliox 3% *vs* placebo 24%, p<0·01), but this was an observational study. By contrast, a multicentre randomised trial by Jolliet and colleagues[29] of 72 h of continuous heliox versus air–oxygen with NIV in severe hypercapnia COPD exacerbations was stopped early for futility, by not showing a reduction in the need for endotracheal intubation or intensive care unit mortality, as previously reported.[30,31]

Heliox has been suggested as a driving gas for nebulised medications, because it might facilitate movement of smaller drug particle size and greater flow through partially obstructed airways, and therefore might be effectively delivered to distal airways. A systematic review[32] of heliox-driven nebulised bronchodilator therapy in patients with asthma reported a 17·2% improvement in peak expiratory flow, compared with use of oxygen, and a reduction in admissions to hospital. The greatest improvements were noted in the most severe subgroup of patients (peak expiratory flow <50% predicted).[32] Similarly, El-Khatib and colleagues[33] found improvements in spirometry with heliox-driven nebulised bronchodilator therapy, specifically in patients with forced expiratory volume in 1 s (FEV_1) of 50% or less of predicted (p=0·01).

Heliox could serve as a useful bridge therapy in the treatment of upper airway obstruction, but this use has not yet been studied in a randomised trial. Available evidence is insufficient to recommend the use of heliox in the treatment of severe COPD exacerbations. Heliox might be considered for use in mechanically ventilated patients with severe asthma, mild hypoxaemia, and worsening dynamic hyperinflation, despite other therapies. Care must be taken to ensure that the ventilator used is compatible with heliox, since the properties of helium might alter the flow measurements. Because of the high thermal conductivity of helium, ventilators that use hot-wire flow sensors are not compatible with heliox. Scarce preclinical data suggest that heliox might also play a part in the care of patients with ARDS.[34,35] This gas has been shown to decrease work of breathing following extubation.[36] The use of heliox as a driving gas for nebulised medications holds promise, and might be considered for patients who are critically ill and with the most severe obstruction, although further studies are needed. Finally, although it might be beneficial for selected patients with severe acute asthma to prevent intubation, at this time heliox cannot be recommended as a first-line therapy for mechanically ventilated patients with asthma.

Of note is that helium stores are depleting and a call is needed for its increased production. Although the need for heliox is relatively small, helium is essential for other medical applications such as cooling of MRI equipment.

Inhaled nitric oxide for hypoxaemic respiratory failure

Nitric oxide (NO) is a colourless and odourless gas, known to be an environmental pollutant and a toxic component of cigarette smoke. NO is formed endogenously in endothelial cells from L-arginine, catalysed by the enzyme NO synthase. In 1987, NO was identified as the molecule that was previously known as endothelial-derived relaxing factor. Shortly thereafter, studies in both animals and people reported that NO, when inhaled, could decrease pulmonary vascular resistance in patients with pulmonary hypertension without causing systemic vasodilation.[37–39] Inhaled NO (iNO) causes local pulmonary vasodilation by rapidly diffusing across alveolar cells to the neighbouring smooth muscle of pulmonary arterioles, where it activates cyclic GMP (figures 3 and 4). NO binds with high affinity to haemoglobin in the blood, thereby preventing systemic effects. iNO is deemed safe at concentrations less than 80 ppm, with higher concentrations causing side-effects including methaemoglobinaemia, decreased platelet aggregation, pulmonary oedema, and generation of nitrogen dioxide in the gas delivery system.[39–41] High oxygen concentration and residence time with nitrogen oxide in the gas delivery system potentiate the production of toxic nitrogen dioxide. Administration of iNO reduces endogenous NO

production, and the drug should be tapered gradually as rapid discontinuation can cause rebound pulmonary hypertension.[42,43]

iNO has been approved by the US Food and Drug Administration since 1999, for the treatment of only persistent pulmonary hypertension of newborn babies, in whom it increases arterial oxygen concentrations and decreases the need for extracorporeal membrane oxygenation.[44,45] However, clinicians most commonly deliver iNO for ARDS, with an estimated 10–20% of these patients receiving iNO in the course of their treatment.[46,47] Studies[48–50] of iNO in treatment of ARDS have shown a short-term improvement in arterial oxygenation, but no improvement in survival or duration of mechanical ventilation. Adhikari and colleagues[47] did a meta-analysis of 1237 patients with ARDS from 12 randomised controlled trials comparing iNO with control, finding that PaO_2/F_iO_2 increased on day 1 of treatment (mean increase 16 mm Hg) for those receiving iNO, with no effect on mean pulmonary artery pressure or in-hospital mortality. They also reported an increased risk of renal dysfunction with iNO.[47] As ARDS mortality is driven by multiorgan dysfunction, the benefits in improved oxygenation are unlikely to translate to improved mortality. Of note, several early trials of iNO did not use lung-protective mechanical ventilation. Moreover, the effects of adjunctive therapies for respiratory failure are not rigorously studied. Further studies are needed to establish whether iNO is beneficial in subgroups of patients with ARDS—eg, in those with right ventricular failure, patent foramen ovale with right-to-left intracardiac shunt, or substantial intrapulmonary shunting.

iNO might improve outcomes in a subset of cardiac surgical patients with postoperative pulmonary hypertension.[51] Cardiopulmonary bypass, particularly, is associated with a pulmonary endothelial defect and decreased exhaled NO.[52] iNO decreases pulmonary pressures after coronary artery bypass grafting, even in the absence of pre-existing pulmonary hypertension.[51] Additionally, iNO decreases pulmonary vascular resistance and enhances right ventricular stroke volume after congenital heart repair and heart transplantation.[53] iNO is especially useful after implantation of left ventricular assist devices, because this gas decreases pulmonary vascular resistance and supports the right ventricle until cardiac output equilibrates, ultimately leading to increased left ventricular assist device flow.[54] A trial of iNO is recommended before consideration of right ventricular assist device implantation, because insertion can be avoided with good response to iNO.[55] Although iNO might attenuate neutrophil-mediated ischaemia-reperfusion injury after lung transplantation, data are conflicting in this population.[56,57]

Evidence is scarce that iNO improves outcomes in the intensive care unit. However, iNO is clinically useful for temporising severe hypoxaemia, perhaps delaying or obviating the need for extracorporeal membrane oxygenation, and for facilitating safe inter-hospital patient transfer.[58] Additionally, it might be helpful in treating a select group of patients with right ventricular failure due to elevated pulmonary vascular resistance.[59,60] Careful patient selection is key, and particular caution must be exercised in patients with left ventricular dysfunction, because iNO might precipitate pulmonary oedema and worsen ventilation–perfusion mismatch in this group.[61] Future directions include advances in practical delivery, such as electrically generated NO therapy with nitrogen and oxygen from the air.[62] Ongoing studies are investigating the use of iNO in pulmonary embolism (NCT01939301), its effects on dynamic right ventricular function (NCT02220023), and long-term treatment outcomes in chronic lung and pulmonary vascular disease (NCT02267655, NCT01265888).

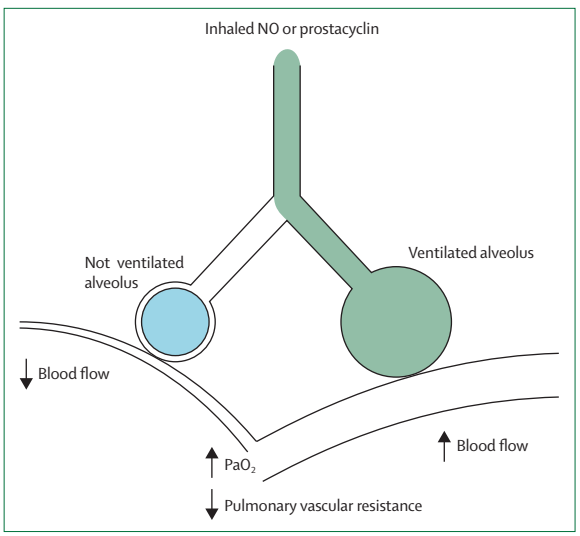

Figure 3: **Selective pulmonary vasodilation**
Inhaled pulmonary vasodilators like nitric oxide (NO) and prostacyclin are selectively delivered to the part of the lung that is ventilated. The result is an improvement in arterial oxygen partial pressure (PaO_2) and a decrease in pulmonary vascular resistance. ↑=increase. ↓=decrease.

Inhaled prostacyclins for hypoxaemic respiratory failure

Endogenous prostacyclin produced by endothelial cells is a prostaglandin in the eicosanoid group of lipids. It functions as an inhibitor of platelet activation and as a vasodilator. Prostacyclin upregulates cyclic AMP (cAMP), triggering smooth muscle relaxation and subsequent vasodilation (figure 4).[63,64] Intravenous synthetic prostacyclin analogues have a non-selective vasodilatory effect and have long been used to treat pulmonary hypertension. Inhaled prostacyclins have a more specific pulmonary vasodilatory effect and can greatly reduce pulmonary artery pressure, improve right ventricular function, and improve oxygenation via improved matching of ventilation–perfusion, as the vasodilatory effect is preferential to well ventilated

regions of the lung. Inhaled prostacyclins have a dose-related physiological effect similar to iNO, have few systemic haemodynamic effects, and are much less expensive than iNO.[65,66] The most common inhaled prostacyclin used in intensive care units is inhaled epoprostenol, and no differences between the two commonly available commercial formulations have been noted.[67] Although inhaled iloprost has similar physiological effects to inhaled epoprostenol, it is less commonly used in the intensive care unit, although case reports[68,69] have suggested feasibility for its use.

Inhaled prostacyclins can not only be used in the chronic treatment of pulmonary hypertension, but also have a reported effect in acute pulmonary hypertension and right ventricular failure. Compared with iNO in patients who had cardiac surgery, no differences were reported in pulmonary artery pressure reduction with a greater reduction in cost with use of inhaled prostacyclins.[70] Similarly, no large differences were noted between the effect of iNO and inhaled prostacyclins in acute right ventricular failure and refractory hypoxaemia in patients who had cardiac surgery and those who had heart and lung transplantation.[71,72]

On the basis of the experience of use with iNO in ARDS, several studies have assessed the use of inhaled epoprostenol in ARDS and refractory hypoxaemia. Clinical studies[65] compared the efficacy and cost of iNO and inhaled epoprostenol in ARDS, finding no difference in the improvement of oxygenation but important cost reduction with use of inhaled epoprostenol. Similar to iNO, although inhaled epoprostenol improves oxygenation in ARDS, it has not been shown to reduce mortality or increase ventilator-free days.[73,74] For these reasons, inhaled prostacyclins are not recommended for routine use in ARDS but can be used to improve oxygenation in patients who are not adequately stabilised with traditional therapies.[75,76] How the effect of inhaled epoprostenol interacts with other rescue measures, such as prone positioning, is unknown, but some animal data suggest an additive benefit.[77]

Inhaled bronchodilators and corticosteroids during mechanical ventilation

Inhaled bronchodilators, including short-acting β agonists (SABAs) and short-acting muscarinic antagonists (SAMAs), have a role in the care of

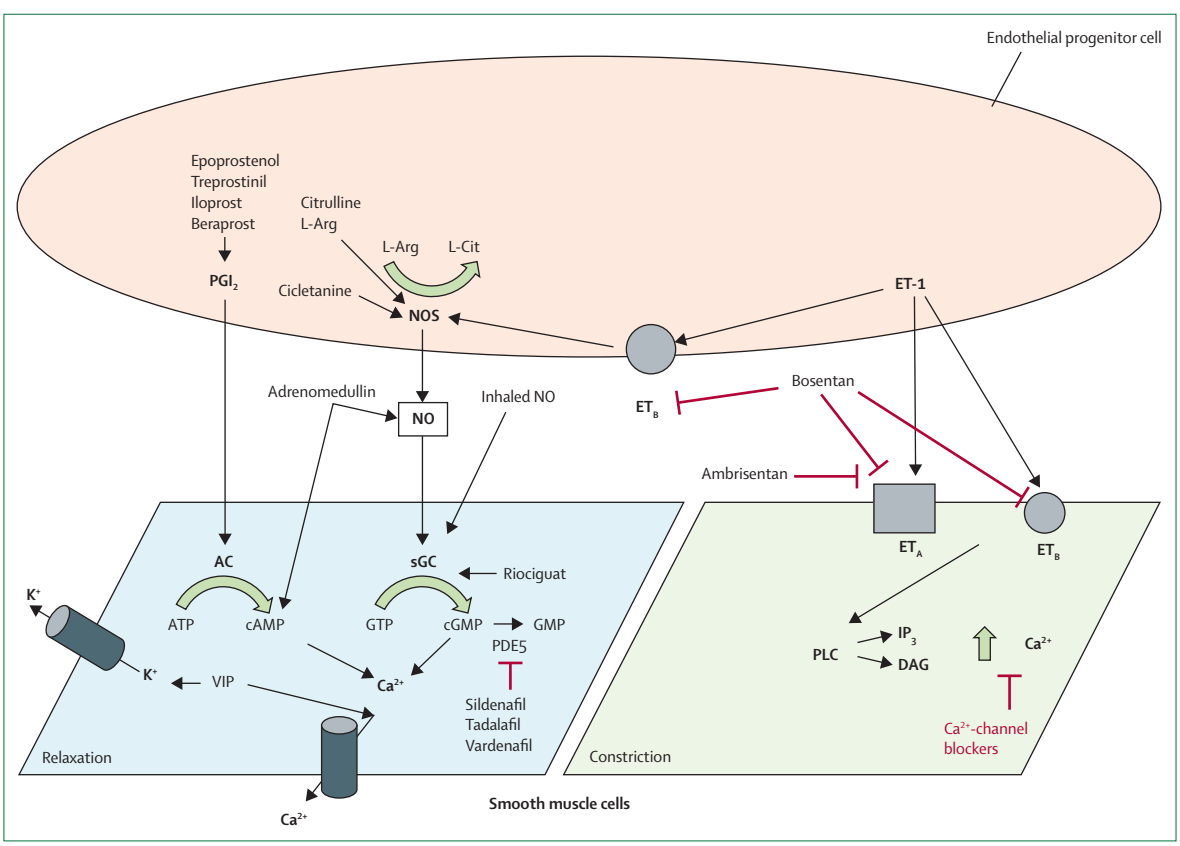

Figure 4: **Sites of action of some endothelial and smooth-muscle cell based therapies**
Arrows indicate activation. PGI_2=prostaglandin I_2. L-Arg=L-arginine. L-Cit=L-citrulline. NOS=nitric oxide synthase. ET-1=endothelin-1. ET_A=endothelin A receptor. ET_B=endothelin B receptor. NO=nitric oxide. sGC=soluble guanylate cyclase. cGMP=cyclic GMP. AC=adenylate cyclase. cAMP=cyclic AMP. PDE=phosphodiesterase (type 5 shown). K^+=potassium channels. DAG=diacyl glycerol. PLC=phospholipase C. IP_3=inositol trisphosphate. Ca^{2+}=calcium. VIP=vasoactive intestinal peptide. T=inhibition. Reproduced from Oishi and colleagues,[64] by permission of Daedalus Enterprises.

mechanically ventilated patients with reversible airflow obstruction. Results of a 2016 international survey[78] indicated that 22% of intubated patients received aerosol therapy, most commonly bronchodilators and steroids.[78] Although commonly prescribed, a dearth of evidence is available examining the effectiveness and safety of bronchodilators in this setting. Evidence of reversible airflow obstruction (increased airway resistance), such as in asthma and COPD exacerbations, provides the clearest indication for the use of SABAs and SAMAs in the intensive care unit. The role of these drugs in conditions causing respiratory failure without evidence of airflow obstruction has either not been studied or been shown to not be beneficial. Irrespective of the indication, careful attention to delivery of SABAs and SAMAs is crucial to achieve a therapeutic benefit.

Aerosol therapy can be administered during mechanical ventilation by pressurised metered dose inhalers (pMDIs), jet nebulisers, ultrasonic nebulisers, or mesh nebulisers.[79] Dry powder inhalers and soft-mist inhalers are not currently compatible with mechanical ventilation. Although a 2013 Cochrane review[80] found insufficient evidence to recommend delivery of bronchodilators via pMDIs versus jet nebulisers, in mechanically ventilated patients, there seemed to be a trend towards lower airway resistance with the nebuliser. Jet nebulisers are associated with an increased risk for ventilator circuit contamination[81] and ventilator-associated pneumonia,[82] and have the potential to affect triggering[83] and for tidal volume augmentation.[84] The popularity of pMDIs during mechanical ventilation has waned in the past 5 years because of the cost of available formulations. Mesh nebulisers have become increasingly popular and have the advantages of efficient drug delivery, remaining within the ventilator circuit between treatments, and adding no additional gas flow into the circuit. Factors that affect aerosolised drug delivery during mechanical ventilation are listed in table 1.[79]

SABAs and SAMAs are standard therapy for acute severe asthma and COPD exacerbations requiring mechanical ventilation.[85,86] In a randomised crossover study by Guerin and colleagues,[85] all 18 patients receiving combination SABA/SAMA therapy via either pMDI or jet nebuliser had reductions in airway resistance ($p<0·05$). In a randomised, triple-blind crossover study by Fernandez and colleagues,[87] 12 patients with COPD exacerbation requiring intubation received only a SAMA versus a SABA/SAMA combination. Combination therapy reduced both auto-PEEP and airway resistance ($p<0·05$).[87]

The role of inhaled bronchodilators in conditions other than COPD and asthma is less clear. In a multicentre, phase 3 randomised trial by the ARDS Clinical Trials Network,[88] 282 patients with ARDS receiving mechanical ventilation were randomly assigned to receive aerosolised albuterol (5 mg) or saline placebo every 4 h for a maximum of 10 days. However, this study[88] was stopped early for futility after interim analysis showed no difference in ventilator-free days (primary endpoint) or rates of death before hospital discharge. Heart rates were significantly higher in the albuterol group by 4 beats/min in the first 2 days after randomisation, although dysrhythmia rates were similar between both groups.[88] Another randomised trial[89] of intravenous salbutamol in patients with ARDS was stopped early due to safety concerns, further raising concerns about the use of β agonists in this population.

Inhaled corticosteroids have not been studied specifically in patients requiring mechanical ventilation for exacerbations of COPD and asthma. In a randomised, double-blind trial of non-intubated patients with severe asthma in an emergency department,[90] 94 patients were given either only inhaled albuterol or inhaled albuterol in combination with flunisolide. FEV_1 and peak expiratory flow values were improved in both groups after drug administration, with a greater effect noted in the

	Effect on aerosol delivery
Type and severity of lung disease	Difficult to deliver aerosol to areas of the lungs with severe airway obstruction
Type of aerosol generator (eg, pMDI, jet nebuliser, mesh nebuliser, ultrasonic nebuliser)	Nebulisers can deliver high doses compared with pMDI; nebulisers can be used for continuous aerosol delivery in the setting of severe obstruction; variability in dose delivery of nebulisers from different manufacturers; jet nebuliser fill volume should be 4–5 mL and powered with a flow of 6–8 L/min
Position of aerosol generator within ventilator circuit	Jet nebuliser placed 15 cm proximal to ventilator circuit Y-piece, pMDI placed in spacer proximal to Y-piece, mesh nebuliser at ventilator outlet (proximal to heated humidifier)
Aerosol particle size	Smaller particles are more able to be deposited deeper in the respiratory tract
Ventilatory settings (eg, mode, tidal volume, flow)	Ventilator settings affect aerosol delivery less with pMDI than with nebuliser; better aerosol delivery for lower flow and higher tidal volume if nebuliser is used; greater aerosol delivery with lower bias flow
Conditions in the ventilator circuit (humidification)	Better aerosol delivery in dry gas than with heated humidification
Synchronisation of drug delivery with inspiratory flow	pMDI actuated at the onset of inspiration, less drug waste if the nebuliser is activated only during inspiration
Gas density	Better aerosol delivery with heliox than other gases (eg, oxygen or air)

pMDI=pressurised metered dose inhaler.

Table 1: **Factors affecting aerosol drug delivery during mechanical ventilation**

flunisolide group (p<0·02). Additional studies showing benefit beyond that reported with systemic corticosteroids are needed before inhaled corticosteroids can be recommended in these patients.

Aerosolised bronchodilators with NIV can be administered with jet nebuliser, mesh nebuliser, or pMDI. This delivery of aerosolised bronchodilators can provide a therapeutic effect, particularly if placed between the leak port of the ventilator circuit and the mask.[21] By contrast, for invasive mechanical ventilation the nebuliser is more effective if placed closer to the ventilator. NIV might also confer a mechanical bronchodilator effect, as shown by improved spirometry in asthmatics with escalating applied expiratory pressures[91] without evidence of improved pulmonary drug deposition.[92]

Inhaled bronchodilators should be considered first-line therapy for the treatment of obstructive lung disease in critically ill patients with acute respiratory failure requiring invasive mechanical ventilation or NIV. Optimisation of drug delivery is crucial (table 1). Patients with lung injury and requiring mechanical ventilation for conditions such as ARDS, without evidence of airflow obstruction, should not routinely be administered inhaled bronchodilator therapy. Insufficient evidence exists to recommend inhaled corticosteroid therapy in mechanically ventilated patients.

Aerosolised antibiotics during mechanical ventilation

Aerosolised antibiotics are standard practice for treatment of *Pseudomonas aeruginosa* infection in patients with cystic fibrosis.[93] Ventilator-associated tracheobronchitis and ventilator-associated pneumonia are common in intubated mechanically ventilated patients. There is renewed interest in the use of aerosolised antibiotics for ventilator-associated pneumonia and ventilator-associated tracheobronchitis, fuelled by the emergence of multidrug-resistant pathogens, most often Gram-negative bacteria. Because systemic antibiotics are associated with toxicity, aerosolised antibiotics are attractive either as monotherapy or as an adjunct to intravenous administration. Aerosolised antibiotics include amikacin, amikacin and fosfomycin combination, colistin, ceftazidime, gentamicin, tobramycin, sisomicin, and vancomycin.[94]

Some systemically administered antibiotics, such as colistin and aminoglycosides, have low penetration into the lung parenchyma. In an experimental model of *P aeruginosa* lung infection, animals were treated with either aerosolised or intravenous colistin.[95] After 24 h of treatment, the median colistin peak lung concentration was 2·8 μg/g with aerosolised colistin, but undetected in lung tissue after intravenous infusion; colistin concentrations were greater in lung segments with mild pneumonia than in those with severe pneumonia.[95] In 40 patients with ventilator-associated pneumonia caused by *P aeruginosa*, Lu and colleagues[96] compared aerosolised ceftazidime (15 mg/kg every 3 h) and amikacin (25 mg/kg per day) with intravenous ceftazidime (90 mg/kg per day) and amikacin (15 mg/kg per day). Aerosol and intravenous administration produced similar efficacy, but antibiotic resistance was reported only in the intravenous group.[96] In patients with ventilator-associated pneumonia caused by *P aeruginosa* and *Acinetobacter baumannii*, Lu and colleagues[97] provided aerosolised colistin either as monotherapy or combined with intravenous aminoglycosides. Inhaled high-dose colistin was non-inferior to intravenous antibiotics, had a low risk of developing resistance, and did not increase the risk of renal toxicity.

In intubated patients with ventilator-associated tracheobronchitis, Palmer and colleagues[98] randomly assigned 43 patients to receive an aerosolised antibiotic or placebo. Gram-positive bacteria were treated with vancomycin (120 mg in 2 mL saline, every 8 h) and Gram-negative organisms were treated with gentamicin (80 mg in 2 mL saline, every 8 h). Systemic antibiotics were administered at the discretion of the responsible physician.[98] The group who received aerosolised antibiotics had reductions in signs of respiratory infection, clinical pulmonary infection score, white blood cell count at day 14, bacterial resistance, and systemic antibiotic use, along with an increased rate of ventilator liberation.[98]

In a double-blind placebo-controlled study[99] that enrolled 42 intubated patients with signs of respiratory infection, aerosolised antibiotics or placebo were given for 14 days or until extubation. Aerosolised antibiotics included vancomycin, gentamicin, and amikacin; systemic antibiotics were not controlled by the study protocol.[99] Aerosolised antibiotics eradicated 26 of 27 organisms present at randomisation, compared with two of 23 organisms with placebo.[99] Aerosolised antibiotics eradicated the original resistant organism on culture and Gram stain at the end of treatment in 14 of 16 patients compared with one of 11 patients receiving placebo.[99] New drug resistance to aerosolised antibiotics did not occur.[99] Compared with aerosolised antibiotics, resistance to systemic antibiotics increased in those receiving placebo.

Zampieri and colleagues[100] undertook a meta-analysis of aerosolised antibiotics for ventilator-associated pneumonia. Aerosolised antibiotics were associated with high rates of clinical cure (risk ratio 1·23, 95% CI 1·05–1·43), but were not associated with microbiological cure, patient mortality, duration of mechanical ventilation, length of stay in intensive care unit, or renal toxicity. Similarly, Valachis and colleagues[101] did a meta-analysis of aerosolised colistin in the treatment of ventilator-associated pneumonia. A significant improvement was noted in clinical response (odds ratio 1·57, 95% CI 1·14–2·15), microbiological eradication (1·61, 1·11–2·35), and infection-related mortality (0·58, 0·34–0·96) with aerosolised colistin added to intravenous treatment. This

combination did not affect overall mortality (0·74, 0·54–1·01) or nephrotoxicity (1·18, 0·76–1·83).[100]

Use of aerosolised antibiotics for ventilator-associated pneumonia and ventilator-associated tracheobronchitis shows promise. However, wide variability exists in their delivered dose, depending on the amount of antibiotic placed in the nebuliser, nebuliser type, and ventilator settings. Even if the methods from clinical trials are precisely replicated, the delivered dose of aerosolised antibiotic might be inaccurate and become subtherapeutic or toxic. Furthermore, the inability of these drugs to be delivered to the most diseased areas of the lung could restrict their use.[102]

Several aerosolised antibiotics are currently in clinical development, which use proprietary formulations and delivery systems. Available evidence supports that high tracheal and parenchymal concentrations are possible with aerosolised antibiotics. Unless a well characterised aerosol delivery system is used, care should be exercised in the administeration of formulations not designed for inhalation by delivery systems not designed for aerosolised antibiotics. Results of a 2016 survey[103] suggest that not only are aerosolised antibiotics administered in 45% of intensive care units in current practice, but also that 79% of health-care workers avoided giving aerosolised antibiotics because of an absence of evidence-based guidelines.

Conclusions

Although inhaled therapies greatly vary in their use in the intensive care unit, their ability to directly target the lungs in various conditions while potentially avoiding adverse systemic events makes them attractive for treatment purposes. Despite this, evidence regarding their use in the intensive care unit has been scarce. Our recommendations for use of inhaled therapies are in table 2. Given the few proven therapies in highly morbid conditions (eg, ARDS, ventilator-associated pneumonia, and pulmonary hypertension), continued research on novel inhaled treatments and outcomes associated with established therapies is warranted.

Ongoing clinical trials are investigating use of different inhaled antibiotics in mechanically ventilated patients, including inhaled amikacin (INHALE1 [NCT01799993] and INHALE2 [NCT00805168]), vancomycin (NCT01925066), colistin (NCT01975350), tobramycin (VAPORISE [NCT02440828]), and the combination of tobramycin and vancomycin (AAINTVAP [NCT02478710]). Inhaled vancomycin is also being tested for eradication of meticillin-resistant *Staphylococcus aureus* lung colonisation (PMEP [NCT01594827]). Additionally, routine use of mucolytics and bronchodilators in mechanically ventilated patients is being tested (NCT02159196), and might help in the assessment of the benefits and risks of these drugs. Delivery of inhaled medications in a preventive manner, such as the treprostinil inhalation for patients at high risk for ARDS (NCT02370095), is being investigated. Drugs that target modulation of host defence or the inflammasome—eg, inhaled granulocyte macrophage-colony stimulating factor for respiratory virus-associated severe pneumonia (NCT02601365), and low-dose inhaled carbon monoxide in ARDS (NCT02425579)—are being studied.

Irrespective of the drug used, an ongoing challenge for any of the inhaled therapies is that often the most diseased lung is the least accessible by the inhaled route. Future research will need to focus on ways to both accurately dose and assess drug response if substantial parallel ventilation heterogeneity exists. Additionally, direct delivery of medications to the lung has the potential to expose the lung epithelium to very high concentrations of medication and possible injury. Thus it will be equally important to develop sensitive measurements of epithelial injury.

	Recommendation
High-flow nasal cannulae	Useful in hypoxaemic, non-hypercarbic respiratory failure; beneficial in the postextubation period; potentially useful for pre-oxygenation during intubation
Heliox	Potentially useful for upper airway obstruction and delivery of bronchodilators in severe obstructive lung disease; avoid use with high F_IO_2 (>0·4) requirement; limited ventilator compatibility
Inhaled nitric oxide	Possible role in right ventricular failure with high PVR, after LVAD and before RVAD placement; role in ARDS limited to rescue therapy (controversial); avoid with severe left ventricular dysfunction
Inhaled prostacyclins	Improves oxygenation in ARDS, but has not been shown to reduce mortality
Aerosolised bronchodilators	Role in obstructive lung disease (asthma and COPD exacerbations); no benefit in ARDS
Aerosolised antibiotics	Possible adjunctive role in VAT/VAP treatment

F_IO_2=fraction of inspired oxygen. PVR=pulmonary vascular resistance. LVAD=left ventricular assist device. RVAD=right ventricular assist device. ARDS=acute respiratory distress syndrome. COPD=chronic obstructive pulmonary disease. VAT=ventilator-associated tracheobronchitis. VAP=ventilator-associated pneumonia.

Table 2: **Summary of author recommendations for inhaled therapies**

Contributors

All authors contributed to the writing of this Series paper, and reviewed and approved submission of the final manuscript.

Declaration of interests

RSH receives consulting fees from Merck for service on a clinical adjudication committee for pneumonia events in a clinical trial. DRH reports personal fees from Philips Respironics, Medtronic Covidien, Bayer, McGraw-Hill, Jones and Bartlett, UpToDate, and the American Board of Internal Medicine. SDL, JWA, KAH, and EKB declare no competing interests.

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