This is the supplement for the manuscript entitled "Oxygenation Strategy in Immunocompromised Patients with Acute Respiratory Failure" submitted to JAMA.

<u>This supplement contains the following items</u>

1. **Pages 2-69: Copies of the study's initial protocol,**
2. **Pages 70-81: Final protocol**
3. **No amendment was performed on the protocol. The only request to the IRB was to add new centres to the study.**
4. **Page 82-83: Copies of the original statistical analysis plan,**
5. **Pages 84-127: Final statistical analysis plan as published in TRIALS**
6. **No amendment was performed on the statistical analysis plan**

INITIAL PROTOCOL (Submitted to the grant application)

A Randomised Controlled Non-Inferiority Trial of High-Flow Nasal Oxygen versus Usual Oxygen Therapy in Critically Ill Immunocompromised Patients

Oxygène à haut débit humidifié chez les patients immunodéprimés en insuffisance respiratoire aigüe : un essai randomisé contrôlé

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This project was prepared for submission to the 2015 PHRC N 15 -15 reviewing process.

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Organisation responsible for quality assurance:

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Organisation responsible for data management and statistics:

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Anticipated number of recruiting centres: 26

CONTENT **Page**

54

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1. Abstract

Background: Acute respiratory failure (ARF) is the leading reason for ICU admission in immunocompromised patients. Usual oxygen therapy involves administering low-to-medium oxygen flows through a nasal cannula or mask [with or without a bag and with or without the Venturi system] to achieve $SpO_2 \geq 95\%$. Based on a landmark trial by Hilbert et al. published in 2001, oxygen therapy is usually combined with non-invasive ventilation [NIV] providing both end-expiratory positive pressure and pressure support. However, in a recent trial by our group (in press), NIV was not superior over oxygen without NIV. High-flow nasal oxygen [HFNO] therapy is a focus of growing attention as an alternative to usual oxygen therapy. By providing warmed and humidified gas, HFNO allows the delivery of higher flow rates [of up to 60 L/min] via nasal cannula devices, with FiO_2 values of nearly 100%. Physiological benefits of HFNO consist of higher and constant FiO_2 values, decreased work of breathing, nasopharyngeal washout leading to improved breathing-effort efficiency, and higher positive airway pressures associated with better lung recruitment. Clinical consequences of these physiological benefits include alleviation of dyspnoea and discomfort, decreases in tachypnoea and signs of respiratory distress, a diminished need for intubation in patients with severe hypoxemia, and decreased mortality in unselected patients with acute hypoxemic respiratory failure. However, although preliminary data establish the feasibility and safety of this technique, HFNO has never been properly evaluated in immunocompromised patients.

Hypothesis: HFNO is not inferior to the usual care [low/medium-flow oxygen and/or NIV] in minimising day-28 mortality.

Design: Randomised multicentre (26 centres) open-label controlled non-inferiority trial.

Intervention: Continuous HFNO only vs. usual care [low/medium-flow oxygen and/or NIV]

Inclusion criteria: Only patients meeting all five of the following criteria can be included: **1**) adult; **2**) known immunosuppression defined as any of the following: a) immunosuppressive drugs/long-term [>3 months] or high-dose [>0.5 mg/kg/day] steroids; b) solid organ transplant; c) solid tumour; d) haematological malignancy; e) HIV infection; **3**) ICU admission for any reason; **4**) oxygen therapy indicated by any of the following: a) respiratory distress with tachypnoea [respiratory rate >30/min]; b) cyanosis; c) laboured breathing; d) $SpO_2 < 90\%$; e) anticipated respiratory deterioration (procedure), **5**) written informed consent from the patient or next of kin. Patients with do-not-intubate orders [DNI] are eligible.

Exclusion criteria: Only patients meeting none of the following criteria can be included: **1**) patient expected, at ICU admission, to die in the ICU; **2**) patient or next of kin having refused study participation; **3**) hypercapnia [which requires NIV, according to current guidelines], **4**) isolated cardiogenic pulmonary oedema [which requires NIV, according to current guidelines], **5**) pregnancy or breastfeeding, **6**) anatomical factors precluding insertion of a nasal cannula; and **7**) no coverage by the French statutory healthcare insurance system.

Primary endpoint: all-cause mortality 28 days after ICU admission

Secondary endpoints: intubation rate, comfort, dyspnoea, respiratory rate, oxygenation, ICU length of stay, ICU-acquired infections, time to resolution of pulmonary infiltrates, oxygen-free survival, ventilation-free survival, re-intubation, lowest median SpO_2 while intubated, mortality after HFNO failure, patient satisfaction, and physician satisfaction

Sample size estimation: Based on an expected 26% mortality rate in the control group, and using a 9% non-inferiority margin, error rate set at 5% and a statistical power at 80%, 408 patients are required in each treatment group [816 patients overall].

Participating centres: 26 centres belonging our study group.

Randomisation: randomised controlled open-label trial (patient as the unit of randomisation).

Study period: 30 months, i.e., 24 months for patient recruitment with 6 months of additional follow-up.

1.bis. Résumé

Introduction: L'insuffisance respiratoire aiguë est la première cause d'admission en réanimation chez les patients immunodéprimés (Idp). L'oxygène (O2) habituellement apporté est de faible à moyen débit, délivré par une sonde nasale ou un masque (avec ou sans réservoir ou système Venturi), avec pour objectif de restaurer une Sp02≥95%. Depuis l'étude de Hilbert, l'O2 est souvent associé à la ventilation non invasive (VNI) apportant aide inspiratoire et pression positive télé-expiratoire. Cependant, un essai récent de notre groupe n'a pas confirmé que la VNI était supérieure à l'O2.

L'oxygène à haut débit humidifié (HFNO) suscite un intérêt croissant et pourrait devenir une alternative à L'O2 *classique*. En effet, le gaz réchauffé et humidifié permet de délivrer jusqu'à 60 L/min de débit au travers d'une sonde nasale, avec une pression partielle en O2 (FiO2) proche de 100%. Les effets physiologiques de l'HFNO consistent en l'apport de Fi02 élevées et constantes, une diminution du travail respiratoire, un rinçage de l'espace mort nasopharyngé, et des pressions positives dans les voies aériennes, permettant un meilleur recrutement alvéolaire. Les conséquences cliniques de ces effets comprennent une diminution de la dyspnée, de la tachypnée, des signes de détresse respiratoire, de l'inconfort, du recours à l'intubation chez les patients les plus hypoxémiques et d'une diminution de la mortalité. Néanmoins, l'HFNO n'a jamais été évaluée chez les patients Idp, où elle a été démontée comme faisable et sans effet néfaste.

Hypothèse : L'HFNO n'est pas inférieure à la prise en charge habituelle (O2 de faible ou moyen débit avec ou sans VNI) concernant la mortalité à J28.

Schéma de l'étude : Essai randomisé contrôlé ouvert de non-infériorité dans 26 services de réanimation.

Intervention : HFNO continue vs. Traitement habituel (O2 de faible/moyen débit avec ou sans VNI)

Critères d'inclusion : **1**) patients adultes ; **2**) Idp connue à type de a) traitements immunosuppresseurs au long cours (>3mois) ou stéroïdes à forte dose (>0.5 mg/kg/j) ; b) greffe d'organe solide ; c) tumeur solide ; d) hémopathie maligne ; e) infection HIV ; **3**) admission en réanimation quel que soit le motif ; **4**) nécessité d'une oxygénothérapie pour a) tachypnée>30/min ; b) cyanose ; c) tirage respiratoire ; d) Sp02<90% ; e) anticipation d'une aggravation respiratoire (procédure) ; **5**) consentement éclairé par le patient ou ses proches. Les patients avec décision de ne pas intuber sont éligibles pour cet essai.

Critères d'exclusion : **1**) patient moribond ; **2**) refus de participer à l'étude par le patient o ses proches; **3**) hypercapnia (VNI indiquée selon les recommandations en vigueur); **4**) œdème pulmonaire cardiogénique isolé (VNI indiquée selon les recommandations en vigueur); **5**) grossesse ou allaitement ; **6**) barrières anatomiques à l'administration d'une sonde nasale ; **7**) absence de couverture par la sécurité sociale.

Critère de jugement principale : mortalité 28 jours après la randomisation.

Critères de jugement secondaires : recours à l'intubation, confort, score de dyspnée, oxygénation, durée de séjour en réanimation, infections associées aux soins, délai de résolution des infiltrats pulmonaires, nombre de jours vivants sans oxygène et sans ventilation à J28, ré-intubation (HFNO post-extubation), saturation la plus basse pendant l'intubation (HFNO per intubation), mortalité après intubation, et satisfaction des patients et des soignants.

Nombre de sujets nécessaires : attendue une mortalité de 26% dans le bras témoin, et en utilisant une marge de non infériorité de 9%, avec α = 5% et β = 20% (puissance = 80%), 408 patients sont à inclure dans chaque groupe (816 au total).

Centres participants : 26 services de réanimation affiliés au Grrr-OH.

Randomisation : essai randomisé contrôlé ouvert

Durée de l'étude : 30 mois (24 mois de recrutement et 6 mois de suivi).

KEY WORDS

Oxygen

Acute respiratory failure

Immunosuppression

Critical care

Non-invasive

Transplantation

Previous grants [in the frame of DGOS calls] obtained by Elie Azoulay

2001: PHRC Famirea [NEJM 2007]

2005: PHRC MiniMax [CCM 2008, AJRCCM 2009]

2008: PHRC oVNI [ICM 2012, Lancet Oncol 2013]

2009: PHRC Trial-OH [JCO 2013]

2.Background

Acute respiratory failure [ARF] is the leading reason for ICU admission of immunocompromised patients.[1-6] Mortality has decreased dramatically in this population in recent years, for several reasons. Management strategies for the underlying conditions have benefited from a number of innovations such as steroid-sparing agents, watch-and-wait approaches, and targeted therapies.[7, 8] Early ICU admission to permit the use of non-invasive diagnostic and therapeutic strategies has increased survival.[1, 9-11] Finally, the optimal use of non-invasive ventilation [NIV] and the introduction of other oxygenation strategies have improved the management of respiratory dysfunction [Table 1].

Oxygen therapy is the first-line treatment in hypoxemic patients. Oxygen can be delivered using low-flow devices (up to 15 L/min) such as nasal cannulas, non-rebreathing masks, and bag valve masks [Figure 1]. The fraction of inspired oxygen [FiO_2] obtained using these devices varies with the patient's breathing pattern, peak inspiratory flow rate, delivery system, and mask characteristics. Maximum flow rates are limited in part by the inability of these devices to heat and humidify gas at high flows. With conventional medium-flow systems, such as Venturi masks, pressurized oxygen is forced through a small orifice at a constant flow, and this draws in room air through entrainment ports, at a set air/oxygen ratio. Although, compared to conventional nasal systems the FiO_2 value thus obtained is more stable, tolerance is poorer, as the mask is cumbersome and the inspired gas may be inadequately heated and humidified. Also, if the patient has a high inspiratory flow rate, the amount of entrained room air is large and dilutes the oxygen, thereby lowering the FiO_2. Twenty years ago, Dewan and Bell described their experience with 'high flow rates' delivered using a regular nasal cannula in patients with chronic obstructive pulmonary disease.[12]

192 **Table 1: Definitions for oxygen delivery devices and reported outcomes using HFNO**

Definitions	
HFNO	Device that delivers humidified and warmed high-flow oxygen at flows greater than 15 L/min.
Usual oxygen therapy devices	Devices used to treat spontaneously ventilating patients in the ICU who require supplemental oxygen. They deliver either - low-flow oxygen [including nasal cannula, Ventimask® without Venturi effect, and non-rebreather mask] - or medium-flow oxygen [Venturi masks and medium-flow facemasks]
Non-invasive ventilation (NIV)	Administration of ventilatory support without using an endotracheal tube or tracheostomy tube. Ventilatory support can be provided through diverse interfaces (mouthpiece, nasal mask, facemask, or helmet), using a variety of ventilatory modes (e.g., volume ventilation, pressure support, bi-level positive airway pressure [BiPAP; see the image below], proportional-assist ventilation [PAV], and continuous positive airway pressure [CPAP]) with either dedicated NIV ventilators or ventilators also capable of providing support through an endotracheal tube or mask
Clinical outcomes in HFNO studies	**Assessed by measuring**
Oxygenation [desaturation]	Continuous SpO_2 PaO_2 at fixed times PaO_2/FiO_2 ratio
Ventilation	$PaCO_2$
Airway pressures	Nasopharyngeal or hypopharyngeal catheter
Work of breathing	Respiratory rate
Patient comfort and adherence	Visual analogue scale [VAS] for breathing difficulties Satisfaction and tolerance Global comfort Dyspnoea [VAS or Borg scale], dry mouth
Cardiovascular status	Heart rate Shock Need for vasopressors
Complications	Need for NIV Need for intubation and mechanical ventilation [MV] Mortality

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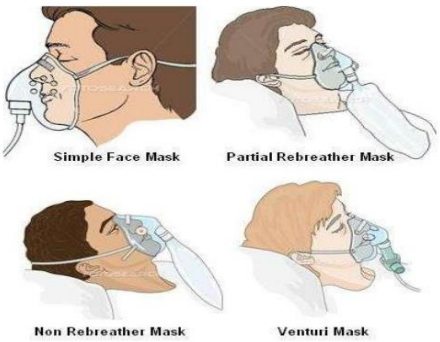
Figure 1: Low-flow and high-flow oxygen delivery devices

Low-flow nasal catheter

Low-flow nasal cannula



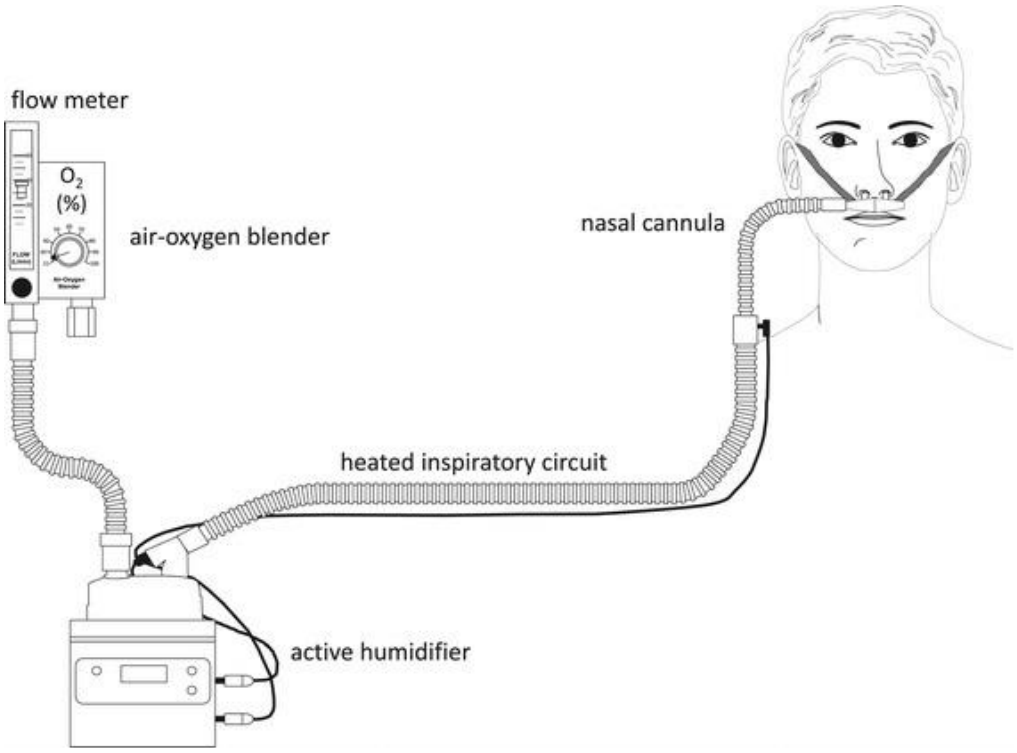
Low-flow and medium-flow masks

Non-invasive ventilation

High-flow nasal cannula

Over the past two decades, devices that deliver heated and humidified oxygen at high flows through a nasal cannula were developed as an alternative to low/medium flow devices. High-flow nasal oxygen [HFNO] delivers oxygen flow rates of up to 60 L/min. An air/oxygen blender is connected via an active heated humidifier to a nasal cannula and allows FiO_2 adjustment independently from the flow rate [Figure 2]. Compared to other devices, HFNO provides a number of physiological benefits including greater comfort and tolerance; more effective oxygenation under some circumstances; and breathing pattern improvements with an increase in tidal volume and decreases in respiratory rate and dyspnoea. These benefits are broadening the indications of HFNO, which has now been evaluated and used to treat hypoxemic respiratory failure and cardiogenic pulmonary oedema, to improve oxygenation for pre-intubation, and to treat patients after surgery or after extubation. HFNO has been used both to prevent pulmonary complications and to treat established respiratory failure. Moreover, recent high-quality randomised controlled trials have confirmed previous preliminary results.[13,14] Nevertheless, controlled studies in specific patient populations, such as immunocompromised patients, are needed to confirm that HFNO is clinically superior over other methods, to evaluate effects on survival, and to determine the optimal indications of HFNO compared to other modalities such as standard oxygen therapy and NIV.

Figure 2: High-flow nasal oxygen [HFNO] device. An air/oxygen blender, allowing FiO_2 values ranging from 0.21 to 1.0, generates flow rates of up to 60 L/min. The gas is heated and humidified by an active heated humidifier and delivered via a single limb.



3. Drawbacks associated with usual oxygen therapy

Low/medium-flow oxygen is the first-line treatment for hypoxemic patients and is generally provided via a face mask or nasal cannula. These delivery devices have several drawbacks that limit the efficacy and tolerance of the oxygen therapy (Table 2). Low-flow oxygen is usually not humidified and therefore often causes distressing symptoms such as dry nose, dry throat, and nasal pain. Bubble humidifiers are often used to humidify gas delivered to spontaneously breathing patients but fails to eliminate all discomfort when absolute humidity is low.[15,16] In addition to insufficient humidification, insufficient warming of the inspired gas causes patient discomfort. Symptom severity increases with flow. Thus, oxygen cannot be delivered at flows greater than 15 L/min. However, in patients with respiratory failure, inspiratory flows vary widely and are considerably higher, between 30 and more than 100 L/min. As a result FiO_2 values are variable and often lower than needed.

240 **Table 2: Drawbacks of standard oxygen therapy that limit the effectiveness and**

241 **tolerance of oxygen delivery**

Oxygen is not humidified at low flow - dry nose - dry throat - dry mouth - nasal pain - ocular irritation, - nasal and ocular trauma - discomfort related to the mask - gastric distension - aspiration - global discomfort
Insufficient heating leads to poor tolerance of oxygen therapy
Unwarmed and dry gas may cause bronchoconstriction and may decrease pulmonary compliance and conductance.
With low/medium-flow devices, oxygen cannot be delivered at flows greater than 15 L/min, whereas inspiratory flow in patients with respiratory failure varies widely and is considerably higher, between 30 and more than 100 L/min.
Given the difference between the patient's inspiratory flow and the delivered flow, FiO_2 is both variable and often lower than needed.

242

4. Physiological effects of HFNO

HFNO may have several advantages over low/medium-flow oxygen delivery systems, resulting in better physiological effects. The mechanisms through which HFNO devices affect the respiratory system and alter gas exchanges are still under investigation, but a growing body of evidence supports those outlined below [Table 3].

1/ HFNO delivers higher and more stable FiO_2 values

In healthy volunteers, HFNO with flow rates >15 L/min produced higher FiO_2 values [measured using a nasal catheter placed behind the uvula] to the alveoli, compared to a low-flow nasal cannula.[17] HFNO maintains high FiO_2 values by delivering flow rates higher than the spontaneous inspiratory demand, thereby diminishing room-air entrainment, which occurs commonly with standard nasal cannulas and face masks. Among all other oxygen delivery devices, only the Venturi mask at its maximum flow rate can deliver stable FiO_2 values across a wide range of respiratory rates.[18] As the difference between the patients' inspiratory flow and the delivered flow is small with HFNO, FiO_2 remains relatively stable. However, the flow rate must be set to match the patient's inspiratory demand and/or the severity of respiratory distress.

2/ HFNO washes out the nasopharyngeal dead space

This effect has several benefits.

- It increases the fraction of minute ventilation that penetrates into the alveoli and participates in gas exchange.[12] However, this effect reaches a plateau above a threshold flow rate corresponding to complete washout of the nasopharyngeal dead space.
- It improves respiratory efficiency.[19]
- It improves thoraco-abdominal synchrony. In a study that used respiratory inductance plethysmography, thoraco-abdominal synchrony was better with HFNO than with facemask oxygen therapy.[20] Furthermore, HFNO was associated with a lower respiratory rates and similar

tidal volume [VT], indicating a decrease in minute ventilation; as well as with a similar $PaCO_2$ value, suggesting that alveolar ventilation was unchanged. Lower respiratory rates with HFNO than with low-flow oxygen have also been documented in clinical studies.[21-23]

3/ HFNO decreases the work of breathing

HFNO decreases the work of breathing by mechanically stenting the airway.[24] Also, the high flow of oxygen matches the patient's inspiratory flow and markedly decreases the inspiratory resistance associated with the nasopharynx and, therefore, the attendant work of breathing. This change in resistance that translates into a decrease in the resistive work of breathing is as efficient as nasal continuous positive airway pressure [CPAP] set at 6 cmH_2O.[12,25]

4/ HFNO provides warm humidified gas

Low/medium-flow oxygen devices delivering dry and unwarmed gas are associated with mask discomfort, nasal and oral dryness, ocular irritation, nasal and ocular trauma, gastric distension, and aspiration.[15,16] Unwarmed and dry gas may cause bronchoconstriction and decreases in pulmonary compliance and conductance.[26,27] The provision by HFNO of adequately warmed and humidified gas to the conducting airways improves conductance and pulmonary compliance compared to dry, cooler gas.[31, 32] In a bench study, two HFNO devices delivered adequately warmed and humidified gas at flows of 40 L/min or more, regardless of VT and minute volume.[28]

The delivery of warm humidified gas reduces the work of breathing and improves mucociliary function, thus facilitating secretion clearance, decreasing the risk of atelectasis, and producing a good ventilation/perfusion ratio and better oxygenation.[29]

Under normal conditions, the nasal passages warm and humidify the inspired air to 37°C and 100% of relative humidity.[30] Therefore, by warming and humidifying the inspired gas, HFNO probably decreases energy costs.

5/ *HFNO increases positive airway pressures*

HFNO has been shown to increase positive airway pressures in studies involving measurements of nasal pharyngeal pressure, oral cavity pressure, end-expiratory oesophageal pressure, and tracheal pressure.[33,34] High flow through the nasopharynx can be titrated to produce a positive distending pressure, thereby improving lung recruitment and decreasing the ventilation-perfusion mismatch in the lungs. Nasal cannula size is a critical determinant of CPAP generation, as the positive pressure level depends in part on air leakage around the cannula prongs.[35] Typically, the nasal cannula can generate positive pressure levels of up to 8 cm H_2O in the pharynx.[36] Airway pressure is significantly higher when breathing with the mouth closed than with the mouth open. In healthy adults, inspiratory and expiratory pharyngeal pressures were linearly related when flow rates were increased to 60 L/min.[33] In a study of patients after heart surgery, HFNO at 35 L/min delivered low levels of positive airway pressure.[34] The importance of minimising leaks around the nares has been demonstrated.[37]

Although the positive end-expiratory pressure [PEEP] generated by HFNO is relatively low compared to that seen with closed systems, it can increase the lung volume and recruit collapsed alveoli.[17,34,36,38] A study involving electrical lung impedance tomography in patients after heart surgery documented larger end-expiratory lung volumes with HFNO than with low-flow oxygen therapy.[21] In healthy adults, the same measurement method showed that HFNO increased the end-expiratory lung volume in the prone and supine positions, compared to breathing ambient air.[38]

313 **Table 3: Physiological benefits of HFNO compared to conventional oxygen therapy**

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FiO_2 values are higher and more stable because the delivered flow rate is higher than the spontaneous inspiratory demand and because the difference between the delivered flow rate and the patient's inspiratory flow rate is smaller. ☞ The flow rate must be set to match the patient's inspiratory demand and/or the severity of the respiratory distress.
The anatomical dead space is decreased, via washout of the nasopharyngeal space Consequently, a larger fraction of the minute ventilation reaches the alveoli, where it can participate in gas exchange. Respiratory efforts become more efficient. Thoraco-abdominal synchrony improves.
The work of breathing is decreased because HFNO mechanically stents the airway, provides flow rates that match the patient's inspiratory flow, and markedly attenuates the inspiratory resistance associated with the nasopharynx, thereby eliminating the attendant work of breathing.
The gas delivered is heated and humidified Warm humid gas reduces the work of breathing and improves muco-ciliary function, thereby facilitating secretion clearance, decreasing the risk of atelectasis, and improving the ventilation/perfusion ratio and oxygenation. The body is spared the energy cost of warming and humidifying the inspired gas. Warm humid gas is associated with better conductance and pulmonary compliance compared to dry, cooler gas. ☞ HFNO delivers adequately warmed and humidified gas only when the flow rate is >40 L/min.
Positive airway pressures are increased The nasal cannula generates continuous positive pressures in the pharynx of up to 8 cm H_2O. The positive pressure distends the lungs, ensuring lung recruitment and decreasing the ventilation-perfusion mismatch in the lungs. End-expiratory lung volume is greater with HFNO than with low-flow oxygen therapy. ☞ Minimising leaks around the cannula prongs is of the utmost importance.

315

5. Clinical trials in adults with hypoxemic respiratory failure

We searched for publications and abstracts in PubMed, Embase, and the Cochrane Database of Systematic Reviews using the MeSH headings 'oxygen inhalation therapy' OR 'positive pressure respiration' AND the text words 'high flow nasal' OR 'nasal cannula' OR 'nasal prong.' We limited our search to publications in English reporting studies in humans. In adults, high-flow oxygen devices are expected to improve respiratory function in a variety of clinical settings including pulmonary oedema, chronic obstructive pulmonary disease [COPD], sleep apnoea, pre-oxygenation for intubation, post-extubation respiratory failure, mild-to-severe acute respiratory distress syndrome [ARDS], and patients with DNI orders.

As shown in Tables 4 and 5, several studies conducted in the past decade evaluated the potential clinical benefits of HFNO in ICU patients. Moreover, HFNO was assessed in high-quality clinical trials in various settings and patient populations in the last two years.[13,14,39-42]

Table 4 reports the outcomes of HFNO therapy in patients with acute hypoxemic respiratory failure in the ICU or emergency department. HFNO was consistently found to alleviate respiratory distress (decreases in laboured breathing, respiratory rate, and thoraco-abdominal asynchrony) and to improve comfort and oxygenation (usually assessed by SpO_2 but also in some studies by the PaO_2/FiO_2 ratio or oxygen flows). Interestingly, HFNO proved feasible in patients with ARDS, obviating the need for intubation in 60% of cases.[43] In other studies, HFNO decreased the need for intubation or NIV.[44] Important information was obtained from a cohort of 175 patients with hypoxemic ARF requiring intubation after HFNO failure.[42] Patients intubated within 48 hours of HFNO initiation had a significantly lower ICU mortality rate [39.2% vs. 66.7% in patients intubated after at least 48 hours of HFNO, P=0.001], a higher extubation success rate [37.7% vs. 15.6%, P=0.006], and a higher number of ventilator-free days. The FLORALI study is a large, multicentre, randomised, controlled, trial with clinical

endpoints that compared HFNO to usual oxygen therapy and to NIV in unselected patients with hypoxemic ARF.[13] This landmark study established the clinical benefits of HFNO in this population. Although the overall intubation rate was not significantly different across the three groups [38% with HFNO, 47% with usual oxygen, and 50% with HFNO+NIV], significantly fewer patients with severe hypoxemia required intubation in the HFNO group, and the number of ventilator-free days by day 28 was significantly higher in the HFNO group. Most importantly, 90-day mortality was significantly lower in the HFNO group than in the other two groups. This study suggests a role for HFNO in the usual care of unselected ICU patients with hypoxemic ARF and also raises concerns about the safety of NIV in this population. Because the primary endpoint [intubation rate] was not significantly influenced by HFNO overall, and given the concerns raised by the HFNO+NIV combination, confirmatory studies may be warranted. Also, neutropenic patients and bone marrow transplant [BMT] recipients were excluded from this trial, although they may account for about 40% of immunocompromised patients and only 10-15% of patients overall had immunosuppression. Among critically ill patients, those with immunosuppression have higher intubation and mortality rates, with substantial changes in recent years.[5] Furthermore, based on evidence of survival benefits with NIV, there is a grade A recommendation to use NIV in immunocompromised patients with ARF.[9] A study specifically focussed on patients with immunosuppression is therefore needed.

Last, two studies demonstrated clinical benefits from HFNO in patients with hypoxemic ARF during bronchoscopy.[45, 46] In both studies, HFNO improved oxygenation during and after the procedure.

362 **Table 4: Clinical studies on HFNO therapy in adults with hypoxemic acute respiratory failure [ARF]**

Reference	Study design	Population	N patients	Results
Hypoxemic acute respiratory failure in the ICU				
[22]	Cohort, unselected patients. HFNO 50 L/min vs. face mask oxygen	Hypoxaemic ARF	38	Improved oxygenation Decreased respiratory rate
[23]	Cohort, unselected patients. HFNO 20-30 L/min vs. face mask oxygen	Hypoxaemic ARF	20	Improved oxygenation Decreases in respiratory/heart rates, dyspnoea, respiratory distress, and thoraco-abdominal asynchrony
[44]	HFNO compared to face mask oxygen	Hypoxaemic ARF	60	Decreased treatment failure (defined as need for NIV) from 30% to 10%. Fewer desaturation episodes
[48]	Cohort study, HFNO 20-30 L/min vs. face mask oxygen	Hypoxaemic ARF	20	Improved comfort; Improved oxygenation
[49]	Cohort study (post hoc)	Hypoxaemic ARF (2009 A/H1N1v outbreak)	20	9/20 (45%) success (no intubation). All 8 patients on vasopressors required intubation within 24 hours. After 6 hours of HFNO, non-responders had lower PaO_2/FiO_2 values and needed higher oxygen flow rates.
[43]	Observational, single-centre study	ARDS	45	40% intubation rate. HFNO failure associated with higher SAPSII, development of additional organ failure, and trends toward lower PaO_2/FiO_2 values and higher respiratory rates
[13]	Multicentre, open-label RCT with 3 groups: HFNO, usual oxygen therapy (face mask), or non-invasive positive-pressure ventilation.	Hypoxaemic ARF, $PaO_2/FiO_2 \leq 300$	310	Intubation rate was 38% with HFNO, 47% with standard oxygen, and 50% with NIV. The number of ventilator-free days by day 28 was significantly higher with HFNO. Decreased D-90 mortality with HFNO
[50]	Retrospective before/after study of HFNO	Hypoxaemic ARF	172	Reduced need for ventilation (100% vs 63%, $P<0.01$) and decreased ventilator-free days.
[42]	Patients intubated after HFNO	Hypoxaemic ARF	175	In patients intubated early, lower mortality (39.2 vs. 66.7 %), higher extubation success (37.7% vs. 15.6 %) and more ventilator-free days. Early intubation was associated with decreased ICU mortality.
Hypoxemic acute respiratory failure in the ED				
[51]	Patients with ARF (>9 L/min oxygen or clinical signs of respiratory distress)	Hypoxaemic ARF	17	Decreased dyspnoea and respiratory rate and improved oxygenation
[52]	RCT of HFNO vs. standard oxygen for 1 h	Hypoxaemic ARF	40	Decreased dyspnoea and improved comfort

363

Table 5 recapitulates the clinical studies of HFNO after surgery, after extubation, or before intubation. A recent, large, multicentre, non-inferiority RCT included 830 patients and compared HFNO to BiPAP for preventing or treating ARF after cardio-thoracic surgery.[14] HFNO was not inferior to BiPAP, skin breakdown was more common with BiPAP, and none of the secondary endpoints [including mortality] differed significantly between the two groups.

Six studies [five RCTs] evaluated HFNO after extubation. Among them, only one, performed in obese patients, showed no benefits from HFNO.[39] In the other five RCTs, HFNO improved oxygenation, comfort, and tolerance; and decreased interface displacements, respiratory rate, heart rate, and the need for ventilation. The results from the ongoing OPERA RCT in patients after abdominal surgery can be expected to provide valuable additional data.[53]

Last, two studies of HFNO for pre-oxygenation before intubation produced divergent results. A prospective before/after study compared a non-rebreather with a reservoir bag ['before' period] to HFNO ['after' period] in 101 patients with hypoxemic ARF requiring intubation.[54] During the HFNO period, higher values were found for both the lowest SpO_2 value during intubation (100% vs. 94% during the 'after' period) and the SpO_2 value at the end of pre-oxygenation. The other study was a multicentre RCT of HFNO vs. a high-FiO_2 bag mask (Venturi) in 124 adults who had acute hypoxemia requiring intubation with a PaO_2/FiO_2 ratio <300 and a respiratory rate ≥30/min.[41] No significant differences were found for the lowest SpO_2 during intubation (91.5% vs. 89.5%, p=0.44) or for intubation-related adverse events including desaturation <80% and death.

384 **Table 5: Clinical studies of HFNO in adults before intubation, after extubation, and after surgery**

Reference	Study design	Population	N patients	Outcome measure	Results
After surgery					
[14]	Multicentre RCT of HFNO vs. BiPAP for at least 4 hours per day	Prevention or treatment of ARF after cardio-thoracic surgery	830	HFNO was not inferior to BiPAP. No difference in ICU mortality Skin breakdown more common with BiPAP after 24 hours	
[39]	Cohort	Patients with ARF after heart surgery	20	Lower respiratory rate and less dyspnoea Improved oxygenation	
After extubation [to avoid re-intubation]					
[40]	Single-centre RCT Venturi mask vs. HFNO for 48 h	Patients with PaO_2/FiO_2 ≤300 immediately before extubation	105	Improved oxygenation and comfort Fewer patients had interface displacements. Fewer patients required re-intubation or NIV.	
[47]	RCT of HFNO until day-2 vs. face mask oxygen	Heart surgery patients ready for extubation	340	Fewer patients needed escalation of respiratory support to NIV.	
[55]	Randomised cross-over study of HFNO vs. Venturi	Patients ready for extubation	50	Tolerance was better with HFNO.	
[52]	Randomised cross-over study of HFNO vs. non-rebreather mask	Patients ready for extubation	17	Less dyspnoea Lower respiratory and heart rates	
[39]	RCT of HFNO vs. usual care	Patients with a BMI≥30 ready for extubation after heart surgery	155	No difference in atelectasis scores on Day 1 or 5, mean PaO_2/FiO_2 ratio, respiratory rate, or re-intubation	
[56]	Retrospective study of HFNO vs. non-rebreather face mask	Patients ready for extubation	67	Improved oxygenation Fewer patients required re-intubation. No difference in mortality	
Before intubation [for oxygenation]					
[54]	Before-(non-rebreather bag-reservoir mask) after (HFNO) study	Adults with acute hypoxemia requiring intubation	101	Higher lowest SpO_2 value during intubation (100% vs. 94%) Higher SpO_2 value at the end of pre-oxygenation	
[41]	Multicentre RCT of HFNO throughout the procedure vs. O_2 mask	Adults with acute hypoxemia requiring intubation, PaO_2/FiO_2<30, and respiratory rate ≥30/min	124	No difference in lowest SpO_2 (91.5 % vs. 89.5%, p=0.44). No difference in intubation-related adverse events including desaturation <80%, and mortality	

385

6. Strengths and weaknesses of published data on HFNO

A growing body of evidence suggests that HFNO therapy may be effective for the early treatment of adults with respiratory failure. However, the areas for which conclusive data exist and those requiring further investigation need to be identified.

At least five points deserve attention. First, the wide variability in inclusion criteria creates considerable heterogeneity across published studies. For instance, studies of patients with hypoxaemia included all patients with hypoxaemia, patients with hypoxaemia and respiratory distress, or patients with a PaO_2/FiO_2 ratio <300. Second, the primary endpoints used in some studies were improvements in physiological variables (oxygenation or lung volumes), which do not always translate into better clinical outcomes (less respiratory distress, less intubation, or better survival). Third, the HFNO parameters (flow rate, FiO_2, time of HFNO exposure) varied in most studies, precluding an assessment of a possible dose-response effect. Fourth, the magnitude of the benefits from HFNO (odds ratio) on the various endpoints [oxygenation, comfort, intubation, or survival], varied markedly across studies. This point is related to the previous one, as dose may influence the effect size. Furthermore, the time of endpoint evaluation also varied. Finally, and importantly, a variety of comparators were used, including low-flow oxygen, Venturi mask, and NIV. This last point is a major source of bias and reflects the current uncertainty about what should be the reference or "standard" for oxygen therapy in patients with acute hypoxaemia.

The therapeutic effect of HFNO may stem from the humidification and/or warming of the inspired gas, high flow, high FiO_2, continuous use (as opposed to intermittent use with NIV), or any combination thereof. Usual care generally involves oxygen delivery via a face mask or nasal cannula, at flows no higher than 15 L/min. Therefore, the improved oxygenation (higher SpO_2 or PaO_2 values) seen with HFNO may be simply a pharmacological effect of the high

flow of oxygen. Moreover, when there are large differences between the patient's inspiratory flow and the delivered flow, FiO_2 values are difficult to control and usually lower than predicted. HFNO, however, effectively delivers high flows with actual FiO_2 values that are usually close to those delivered by the device.[36] These considerations emphasise the importance of using clinical endpoints such as the intubation rate or mortality, rather than physiological endpoints such as SpO_2 or PaO_2/ FiO_2.

A fundamental difference between HFNO and NIV is that HFNO systems maintain a fixed flow and generate variable pressures, whereas many NIV systems use a variable flow to generate a fixed pressure, precluding the manipulation of alveolar ventilation. Another major difference is that the anatomical dead space is increased by NIV interfaces and decreased by HFNO interfaces. With the open HFNO circuit VT cannot be actively increased. Nevertheless, HFNO helps patients by improving alveolar ventilation and decreasing the anatomical dead space. Given these considerations, when comparing HFNO to NIV[13] or BiPAP,[14] in addition to oxygenation and comfort, volume ventilation and pressures (expiratory VT and peak pressures) should be carefully monitored in both groups to determine whether improvements in these parameters in the HFNO group are related to HFNO or to high-volume ventilation in the control group responsible for deleterious effects due to volutrauma.

7. HFNO in immunocompromised patients

Among patients with ARF, those with immunosuppression have higher mortality rates compared to unselected patients. The use of endotracheal mechanical ventilation is associated with higher mortality in immunocompromised patients. Therefore, management techniques that decrease the need for intubation may hold promise for decreasing mortality.

Four studies evaluated the feasibility and safety of HFNO in immunocompromised patients with ARF. In a retrospective single-centre study reported in 2013, the feasibility of HFNO was evaluated in 45 patients with haematological malignancies, chiefly acute myeloid leukaemia [46.7%], myelodysplastic syndrome [13.3%], and lymphoma [11.1%].[57] There was a history of bone marrow transplantation in 21 [46.7%] patients, recent systemic chemotherapy in 22 [48.9%] patients, and current neutropenia in 19 [42.2%] patients. HFNO therapy was titrated to provide a FiO_2 that maintained PaO_2 >90% and a flow of up to 45-50 L/minute. Of the 45 patients, 15 recovered without intubation [33%]; their hospital mortality rate was 2/15 [13.3%], compared to 26/30 [86.7%] of the patients who failed HFNO and required intubation, although the APACHE II score on the day of HFNO initiation was not significantly different between the two groups. HFNO failure was significantly associated with bacterial pneumonia as the cause of ARF. In a single-centre study of patients with solid tumours reported in 2011, of 183 patients taken at random from the institutional database, 132 [72%] had received HFNO in the ICU to treat hypoxia.[58] Among them, 41% improved and 44% remained stable while on HFNO, whereas 15% declined. A 2013 report describes a study in 30 patients with advanced cancer and persistent dyspnoea that used a randomised design to compare the physiological effects of HFNO versus BiPAP for 2 hours.[59] Both treatments similarly improved the dyspnoea, as assessed using a visual analogue scale and the modified Borg scale, and non-significantly diminished the respiratory rate. Oxygen saturation improved only with HFNO. Neither

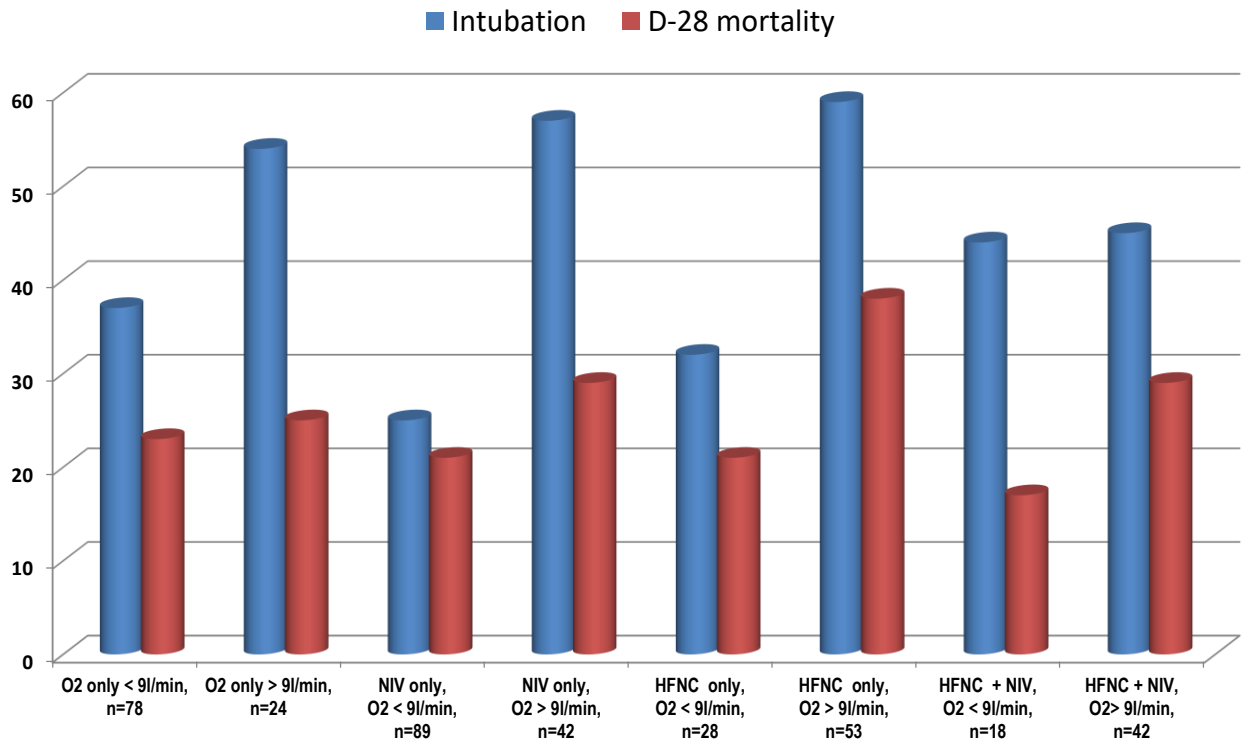
technique induced major adverse effects. The last study, published in 2015, evaluated HFNO for treating ARF requiring ICU admission in 37 lung transplant recipients.[60] HFNO proved feasible and safe and decreased the absolute risk of intubation by 29.8%, with a number-needed-to-treat to avoid one intubation of 3. Last, in a study of 50 DNI patients with hypoxemic respiratory distress, including a third of immunocompromised patients, HFNC allowed an improvement in oxygenation and decreased respiratory rate.[61],

8. Preliminary results from our study group

The first study, by Mokart et al., analysed a retrospective cohort of 178 patients with cancer and ARF (O_2>9 L/min), including 76 (43%) treated with NIV+HFNO, 74 (42%) with NIV+low/medium-flow O_2, 20 (11%) with HFNO alone, and 8 with low/medium-flow O_2 alone.[62] NIV+HFNO was associated with lower mortality (37% vs. 52% in remaining patients, p=0.04) and was independently associated with lower day-28 survival in a propensity-score analysis. Last, in a sub-study of data from our recent iVNIctus RCT of early NIV in immunocompromised patients with ARF,[63] 141/374 (38%) patients received HFNO, and either NIV or low/medium-flow oxygen was used in the other patients. To allow accurate adjustment, we built a propensity score using variables available at ICU admission. Intubation rate and day-28 mortality were not significantly different in the HFNO arm compared to the NIV or low/medium-flow oxygen arm. However, as shown in Figure 3, neither the intubation rate nor the day-28 mortality was higher in the group given HFNO+NIV.

Although the effects of HFNO have varied across studies, the data establish that this treatment modality is feasible and safe in immunocompromised patients. They also demonstrate that outcomes with HFNO are at least as good as with other oxygen therapy methods in this population. Thus, they warrant further trials to determine whether HFNO improves survival in unselected immunocompromised patients with hypoxemic ARF.

Figure 3: Data from our recent trial on the use of HFNO in immunocompromised patients



9. What is the standard of care for providing oxygen to immunocompromised patients? NIV is not superior over low/medium-flow oxygen

The answer to this question has been provided by the iVNIctus trial, completed by the Grrr-OH in January 2015 and recently accepted for publication. This multicentre randomised trial was performed in 26 ICUs to determine whether early NIV improved survival in immunocompromised patients with non-hypercapnic hypoxaemic ARF. Patients were randomly assigned to early NIV or low/medium-flow oxygen therapy alone. HFNO was allowed in both groups, if deemed appropriate by the physician in charge. The primary outcome was day-28 mortality.

Of the 374 enrolled patients, 191 were assigned to early NIV and 183 to oxygen only. At randomisation, median [interquartile range] oxygen flow was 9 [5-15] L/min in the NIV group and 9 [6-15] L/min in the oxygen group. All patients in the NIV group received the first NIV session immediately after randomisation. On day-28 after randomisation, 46 [24.1%] deaths had occurred in the NIV group vs. 50 [27.3%] in the oxygen group [p=0.47]. Oxygenation failure occurred in 155 [41.4%] patients overall, 73 [38.2%] in the NIV group, and 82 [44.8%] in the oxygen group [p =0.20]. There were no significant differences in ICU-acquired infections, duration of mechanical ventilation, or lengths of ICU or hospital stays. These results demonstrate that, in immunocompromised patients admitted to the ICU with hypoxemic ARF, early NIV does not reduce day-28 mortality compared to oxygen therapy alone. The standard of care for oxygenation in critically ill immunocompromised patients should thus be either low/medium-flow oxygen or NIV, as decided by the physician. Last, as mentioned above (in the section on preliminary data from our study group), HFNO was used in about 40% of the patients overall and was not associated with lower intubation rates or mortality, even after adjustment on confounders.

In sum, the use of HFNO is increasing steadily, based on its ease of use, theoretical advantages over low/medium-flow nasal or face mask oxygen, and clinical data suggesting superiority over other oxygen-delivery systems in unselected patients with hypoxemia. Immunocompromised patients have specific treatment needs, as shown by their 2-fold higher mortality rate after intubation compared to other patients. Data on HFNO in immunocompromised patients are conflicting (see point 8 above). Moreover, NIV+HFNO was harmful in the FLORALI RCT in unselected hypoxemic patients, whereas NIV, even when combined with HFNO, had no deleterious effects in the immunocompromised patients in two other studies.[62,63] Furthermore, data on optimal HFNO modalities are urgently needed.

Thus, a study of the efficacy and safety of HFNO in immunocompromised patients is timely. We therefore designed the present RCT [HIGH], which we are submitting to the 2015 PHRC-N call for projects. This RCT is a non-inferiority study of HFNO versus other oxygenation strategies [low/medium-flow oxygen and/or NIV] in immunocompromised patients requiring oxygen. The primary endpoint is day-28 survival. The patients will be recruited at 26 centres belonging to a research network that specialises in the management of critically ill immunocompromised patients and has a particularly high level of expertise in respiratory care strategies. The control group will receive low/medium-flow oxygen and/or NIV as deemed appropriate by the physician, since the recent large iVNIctus trial by our group did not show any superiority of NIV (on intubation rates or survival). The experimental group will receive continuous HFNO at any time after ICU admission, for pre-oxygenation before intubation, after extubation, and for any ICU procedure that might induce hypoxemia).

10. Participating centres: the *Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique* (Grrr-OH)

All participating centres belong to the Grrr-OH, a research network specialising in the respiratory care of critically ill immunocompromised patients. All these centres have previously taken part in observational studies, surveys, or therapeutic trials. They all have high case-volumes of patients with immune deficiencies due to immunosuppressive drugs, solid-organ transplantation, malignancies, or systemic diseases. Although they are specialized in oncology and haematology, they also admit high volumes of patients with systemic diseases, solid organ transplant and other immunosuppression.

All centres are in France, except 14 and 15, which are in Belgium.

533 **Participating ICUs**

534

1	Dr. LEMIALE Virginie	Saint Louis, Paris	Virginie.lemiale@sls.aphp.fr	0142499421	Medical ICU
2	Prof. DEMOULE Alexandre	Pitié-Salpêtrière, Paris	alexandre.demoule@psl.aphp.fr	0142167858	Medical ICU
3	Dr Anabelle Stocklin	IGR, Villejuif	anabelle.stocklin@gustaveroussy.fr	0142114211	Med-Surg ICU
4	Prof. PENE Frédéric	Cochin, Paris	Frederic.pene@cch.aphp.fr	0158414141	Medical ICU
5	Dr. MOKART Djamel	Paoli-Calmettes, Marseille	MOKARTD@ipc.unicancer.fr	04 912479 76	Med-Surg ICU
6	Prof. BOUADMA Lila	Bichat, Paris	lila.bouadma@aphp.fr	0140257707	Medical ICU
7	Dr. KOUATCHET Achille	CHU, Angers	AcKouatchet@chu-angers.fr	0241353655	Medical ICU
8	Prof. DARMON Michael	CHU, St-Etienne	michael.darmon@chu-st-etienne.fr	0477120934	Medical ICU
9	Dr. MOREAU Anne-Sophie	CHRU, Lille	anne.sophie.moreau@gmail.com	032044 48 60	Medical ICU
10	Dr. RABBAT Antoine	Cochin, Paris	Antoine.rabbat@cch.aphp.fr	0158414141	Medical ICU
11	Prof. PAPAZIAN Laurent	Marseille Nord, Marseille	laurent.papazian@ap-hm.fr	0413207116	Medical ICU
12	Dr. SEGUIN Amélie	CHU, Caen	amelie.seguin@free.fr	023822 24 11	Medical ICU
13	Dr. BARBIER François	CHG, Orléans	Francois.barbier@chr-orleans.fr	02385144 44	Med-Surg ICU
14	Prof. BENOIT Dominique	University Hospital, Ghent, Belgium	Dominique.Benoit@ugent.be	+3292606475	Med-Surg ICU
15	Prof. MEERT Anne-Pascale	Jules Bordet, Institute, Brussels, Belgium	ap.meert@bordet.be	+3225413111	Medical ICU
16	Prof. FARTOUKH Muriel	Tenon, Paris	muriel.fartoukh@tnn.aphp.fr	0156016574	Med-Surg ICU
17	Prof. ARGAUD Laurent	Edouard Herriot, Lyon	laurent.argaud@chu-lyon.fr	0472110015	Medical ICU
18	Dr. LEBERT Christine	District Hospital, Les Oudairies	christine.lebert@chd-vendee.fr	0251446470	Med-Surg ICU
19	Dr. BRUNEEL Fabrice	André Mignot, Le Chesnay	fbruneel@ch-versailles.fr	0139639133	Med-Surg ICU
20	Dr. NYUNGA Martine	Victor Provo, Roubaix	Martine.nyunga@ch-roubaix.fr	0320993172	Med-Surg ICU
21	Dr. PEREZ Pierre	Hôpital Brabois, Nancy	p.perez@chu-nancy.fr;	0383154084	Medical ICU
22	Dr. KONTAR Loay	CHU, Amiens	Kontar.Loay@chu-amiens.fr	0322455854	Medical ICU
23	Prof. TAMION Fabienne	CHU Nicolle, Rouen	fabienne.tamion@chu-rouen.fr	0232888261	Medical ICU
24	Dr. GUITTON Christophe	CHU, Nantes	christophe.guitton@chu-nantes.fr	0240375655	Medical ICU

25	**Prof. SCHWEBEL Carole**	**CHU, Grenoble**	**carole.schwebel@chu-grenoble.fr**	**0476767575**	**Medical ICU**
26	**Prof. KLOUCHE Kada**	**CHU, Montpellier**	**k-klouche@chu-montpellier.fr**	**0467336733**	**Medical ICU**

535

Expected number of eligible patients in the participating centres				
#	Investigator	Centre	Expected number of patients recruited per month	Total in 24 months
1	Dr. LEMIALE Virginie	Saint Louis, Paris	3	72
2	Pr. DEMOULE Alexandre	Pitié-Salpêtrière, Paris	2	48
3	Dr Anabelle Stocklin	IGR, Villejuif	1	24
4	Pr. PENE Frédéric	Cochin, Paris	2	48
5	Dr. MOKART Djamel	Paoli-Calmettes, Marseille	2	48
6	Pr. BOUADMA Lila	Bichat, Paris	1	24
7	Dr. KOUATCHET Achille	CHU, Angers	1	24
8	Pr. DARMON Michael	CHU, St-Etienne	1	24
9	Dr. MOREAU Anne-Sophie	CHRU, Lille	2	48
10	Dr. RABBAT Antoine	Cochin, Paris	1	24
11	Pr. PAPAZIAN Laurent	Marseille Nord, Marseille	1	24
12	Dr. SEGUIN Amélie	CHU, Caen	1	24
13	Dr. BARBIER François	CHG, Orléans	1	24
14	Pr. BENOIT Dominique	University Hospital, Ghent, Belgium	1	24
15	Pr. MEERT Anne-Pascale	Jules Bordet, Institute, Brussels, Belgium	1	24
16	Pr. FARTOUKH Muriel	Tenon, Paris	1	24
17	Pr. ARGAUD Laurent	Edouard Herriot, Lyon	2	48
18	Dr. LEBERT Christine	District Hospital, Les Oudairies	1	24
19	Dr. BRUNEEL Fabrice	André Mignot, Le Chesnay	1	24
20	Dr. NYUNGA Martine	Victor Provo, Roubaix	1	24
21	Dr. PEREZ Pierre	Hôpital Brabois, Nancy	1	24
22	Dr. KONTAR Loay	CHU, Amiens	1	24
23	Pr. TAMION Fabienne	CHU Nicolle, Rouen	2	48
24	Dr. GUITTON Christophe	CHU, Nantes	1	24

25	**Pr. SCHWEBEL Carole**	**CHU, Grenoble**	**1**	**24**
26	**Pr. KLOUCHE Kada**	**CHU, Montpellier**	**1**	**24**
	TOTAL	**26 CENTRES**	**34**	**816 PATIENTS**

These numbers were drawn from our recent iVNIctus trial

Of note: We have invited 14 additional centres belonging to the Grrr-OH to participate, and we are awaiting their responses.

11. Study objective and major hypothesis

The **primary objective** of this trial is to determine whether HFNO is not inferior to the usual care for the oxygenation of hypoxemic critically ill immunocompromised patients, regarding all-cause day-28 mortality.

The **secondary study objectives** are to determine whether HFNO is superior over usual-care oxygenation in producing the following outcomes:

- Lower intubation rate (proportion of patients requiring invasive mechanical ventilation) on days 3 and 28;
- Better patient comfort (visual analogue scale [VAS]);
- Less dyspnoea (VAS and Borg scale);
- Lower respiratory rate;
- Better oxygenation (assessed based on the lowest SpO_2 value and on PaO_2/FiO_2 from day 1 to day 3;
- Shorter ICU stay length;
- Lower incidence of ICU-acquired infections;
- Faster resolution of pulmonary infiltrates on chest X-rays (Murray score);
- Higher oxygen-therapy-free and ventilation-free survival rates on day 28;
- Lower re-intubation rate;
- Higher median value of the lowest SpO_2 during intubation;
- Absence of a higher mortality rate in patients intubated after HFNO compared to patients in the control group
- Better satisfaction of the patients and physicians (VASs).

12. Methods: non-inferiority randomised active-controlled design

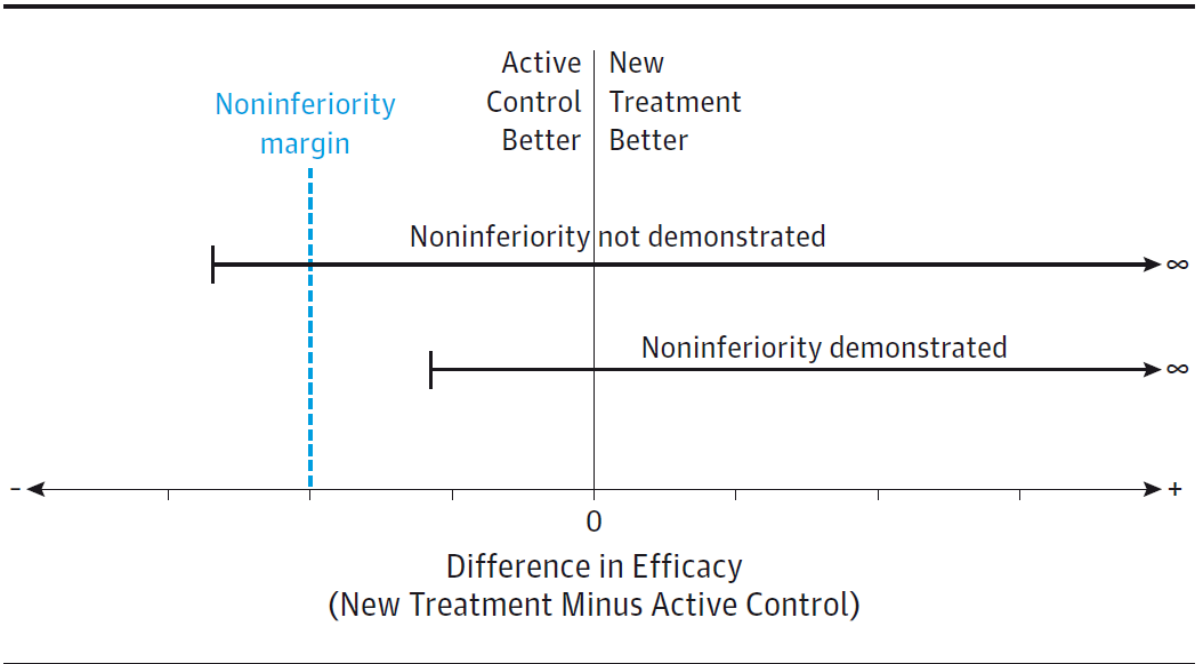
The study aims to evaluate HFNO in immunocompromised patients admitted to the ICU and requiring oxygen therapy. It will use a non-inferiority design.

In the HIGH trial, our goal is not to determine that HFNO is more effective than other oxygenation methods. Instead, we aim to determine whether HFNO is **not inferior** to usual-care oxygenation, because it has other advantages, such as lower cost, lower nurse workload, less patient discomfort, better tolerance, and less skin breakdown. Thus, if HFNO is not inferior to usual-care oxygenation methods, then it would deserve to be used instead of these methods. Although superiority or inferiority of a new treatment can be demonstrated by a superiority trial, an experimental treatment that is not significantly better than the control is not necessarily as good as the control. When a new treatment has known advantages other than better efficacy, then proof that its efficacy is not inferior to that of current treatments is sufficient to warrant its preferential use.

A non-inferiority trial aims at assessing whether the experimental intervention being evaluated is not worse than the control by more than a certain amount, known as the non-inferiority margin (Figure 4).[65] This margin is determined before the study onset, based on what constitutes a clinically important difference, the expected event rates, and, in some cases, regulatory requirements. Other determinants of the non-inferiority margin include the known effect of the control treatment vs. a placebo; disease severity; toxicity, workload, and/or cost of the control treatment; and the primary endpoint. A small non-inferiority margin is usually appropriate if the disease under investigation is severe or if the primary endpoint is death.

Because a non-inferiority trial aims to demonstrate non-inferiority, and not to distinguish non-inferiority from superiority, it uses a one-sided confidence interval. (Figure 4)

Figure 4 adapted from Kaji and Lewis JAMA 2015 [65]: Two different possible results of a non-inferiority trial, summarised by one-tailed confidence intervals for the relative efficacy of the new and active-control treatments



In the top example of Figure 4, the lower boundary of the confidence interval lies to the left of the lower boundary of the non-inferiority margin, indicating that the inferiority in effect versus the control may be larger than the non-inferiority margin. Thus, the new treatment may be worse than the control treatment.

In the bottom example of Figure 4, the lower boundary of the confidence interval lies within the non-inferiority margin, demonstrating non-inferiority of the new treatment relative to the active-control

595 treatment. The overall result of the trial is defined by the lower limit of the one-sided confidence interval
596 rather than by the point estimate for the treatment effect, and the point estimates are therefore not shown.
597
598

We extensively discussed the study design with the study-group physicians at our meeting on July 2, 2015; opinion leaders in the field of acute respiratory failure [REVA network]; and reviewers of the 2015 PHRC-N [who had commented on this point]. We also based our assumptions on results of the trials by Ferrer and Stephan.[14, 66] We agree with the PHRC reviewers that the non-inferiority design is the best option. For all stakeholders, a 9% non-inferiority margin appears clinically relevant. Non-inferiority of HFNO will thus be demonstrated if the lower boundary of the 95% CI is less than 9%.

For all secondary outcomes, we hypothesised that HFNO could be superior over the control. Thus, comparison tests will be used (see below, Statistical section).

Eligible patients are immunocompromised patients who are admitted to the ICU and need oxygen supplementation at any stage of their ICU stay. All randomized patients will be included in the full set of analysis (intent-to-treat basis).

A. Inclusion criteria

- Adult
- Known immunosuppression defined as one or more of the following: (a) immunosuppressive drug or long-term [>3 months] or high-dose [>0.5 mg/kg/day] steroids; (b) solid organ transplantation; (c) solid tumour; (d) haematological malignancy; (e) HIV infection.
- ICU admission for any reason

- Need for oxygen therapy defined as one or more of the following: (a) respiratory distress with a respiratory rate >30/min; (b) cyanosis; (c) laboured breathing; (d) SpO_2<90%; and (e) expected respiratory deterioration during a procedure
- Written informed consent from the patient or proxy

Patients with do-not-intubate [DNI] orders will be eligible.

B. Exclusion criteria

- Patient admitted to the ICU for end-of-life care
- Refusal of study participation by the patient or proxy
- Hypercapnia with a formal indication for NIV
- Isolated cardiogenic pulmonary oedema [formal indication for NIV]
- Pregnancy or breastfeeding
- Anatomical factors precluding the use of a nasal cannula
- Absence of coverage by the French statutory healthcare insurance system

C. Description of the intervention

This open randomised controlled trial will compare two oxygenation strategies.

Usual care [control group]

Patients in the control group will receive the best standard of care, according to the usual practice of the local intensivists and primary-care physicians. Oxygen therapy will be delivered using any device or combination of devices that are part of usual care: nasal oxygen, mask with or without a reservoir bag

and with or without the Venturi system, and NIV. Oxygen settings are set to target an $SpO_2 \geq 95$. HFNO will not be used in the control group. The recent iVNIctus trial [manuscript in press] in immunocompromised ICU patients showed no difference between usual-care oxygen and early NIV in terms of mortality or intubation rates. This finding supports the scientific and ethical acceptability of using either usual-care oxygen or NIV in the control group, according to local protocols and preferences. The reasons for NIV use will be documented in the eCRF. ICU discharge will be allowed when patients will meet the ability to maintain $SpO_2 \geq 95\%$ with less than 2 L/min oxygen.

High-flow nasal oxygen [intervention group]

Patients in the HFNO group will receive the best standard of care, according to the usual practice of the local intensivists and primary physicians, with one exception: supplemental oxygen will be provided only by continuous HFNO. HFNO will be initiated at a flow rate of 50 L/min and 100% FiO_2. If the target SpO_2 is not reached, the flow rate will be increased to 60 L/min. Then, FiO_2 will be tapered to target an $SpO_2 \geq 95$. The minimal flow rate will be 40 L/min. In patients who require intubation, HFNO will be used during laryngoscopy and immediately after extubation. Also, HFNO will be used before, during, and after all ICU procedures. Patients with discomfort due to HFNO will have their flow rate decreased until the discomfort resolves. If the nasal prongs generate significant discomfort or skin breakdown, a Venturi mask will be used instead until HFNO can be used again; except in this situation, neither NIV nor standard oxygen will be used in the intervention group.

HFNO will be stopped based on clinical criteria [improvement of clinical signs of respiratory distress], PaO_2/FiO_2>300, and ability to maintain SpO_2≥95% with less than 2 L/min oxygen via a low-flow device [allowing ICU discharge as HFNO may not be available in the wards].

Patients already receiving HFNO at ICU admission are eligible for this study. Patients intubated at ICU admission become eligible for this study immediately after extubation.

NIV will not be allowed in the experimental group, because the FLORALI study showed higher mortality with HFNO+NIV.

D. Subgroups of interest

Randomisation will be stratified on two factors, namely, hypoxaemia severity [PaO_2/FiO_2<200 vs. ≥200 at randomisation] and any organ dysfunction in addition to the respiratory failure [based on the SOFA score definition]. Thus, analysis could consider treatment-by-subset interaction on such strata.

We have also predefined four subgroups of interest, defined based on factors for which no stratification will be performed though interaction tests are scheduled to be performed. One is the subgroup of patients who required intubation after randomisation and received HFNO during intubation; the outcome measures will be the median lowest SpO_2 during intubation and PaO_2/FiO_2 60 minutes after intubation. Another is the subgroup of patients managed with HFNO after extubation, the outcome measure will be the re-intubation rate. Another is the group of patients who will be intubated in the two groups; the outcome measures will be D-28 mortality as HFNO may have delayed intubation. Finally, we will study the subgroup with DNI orders.

For all these subsets, interaction test between benefit in terms of ICU mortality between the HFNO and control groups, according to the strata, will be performed (See below, the Statistical section for further details on tests).

E. Endpoints

Primary endpoint [non-inferiority of HFNO compared to usual care]

All-cause day-28 mortality

Secondary endpoints [superiority of HFNO compared to usual care]

- Intubation rate [proportion of patients requiring invasive mechanical ventilation] on days 3 and 28
- Patient comfort [VAS score]
- Intensity of dyspnoea [VAS score and Borg scale]
- Respiratory rate
- Oxygenation [based on continuous SpO_2 monitoring, lowest SpO_2 from D1 to D3 and PaO_2/FiO_2 on D1, D2, and D3]
- ICU stay length
- Incidence of ICU-acquired infections
- Time to clear pulmonary infiltrates [Murray score]
- Oxygen-free and ventilation-free survivals [days] by day 28
- Re-intubation rate [for patients who were extubated during the study period]
- Lowest median SpO_2 during intubation [for patients who were intubated during the study period]
- In DNI patients, intubation rate, survival, and comfort

- Mortality in patients intubated after HFNO use [compared with control-group patients]
- Satisfaction of the patients and physicians

F. Possible difficulties, unwanted effects, and safety issues

1. ***Patient recruitment***: We do not anticipate difficulties with patient recruitment, as each ICU admits at least 50 immunocompromised patients per year on average. As reported in the table above, the 26 centres have to include 1 to 2 patients per month to complete the recruitment period within 24 months. Recruitment for the iVNIctus trial by the same group ended 6 months earlier than expected.
2. ***Physician availability to include patients***: The study will require at least 1 hour of work per day at inclusion and 30 minutes on each subsequent study day. During the investigator meeting held to prepare the study design [July 2, 2015], all the investigators expressed keen interest in the study and a firm commitment to making themselves readily available to include patients. The hiring of research assistants [1 day per centre per week] was also perceived very positively by the investigators.
3. ***Ethical and organisational issues***: All the investigators agreed that equipoise was obvious, with low/medium-flow oxygen, NIV, and HFNO being equally appropriate. None of the investigators voiced concern about not using HFNO in half the patients. Also, the conflicting data available so far about the effects of HFNO in immunocompromised patients contributes to the enthusiasm that surrounds this trial. All participating ICUs are fully able to provide immunocompromised patients with the best standard of care.
4. ***Responsibility issues and insurance***: This study uses devices that allow oxygen delivery. low/medium-flow, NIV, and HFNO devices are on the market and are approved for this indication. At

720 present, the choice among these three options is at the discretion of the physician. Thus, our trial comes
721 within the purview of studies of 'usual care' [*soins courants*].
722

13. Hypotheses and expected changes based on the study results

If the study intervention produces beneficial effects

The study intervention is safe, feasible, and effective for providing oxygen to critically ill patients. If the HIGH trial demonstrates non-inferiority of HFNO, then HFNO will deserve preference as this method is associated with better patient comfort, greater dyspnoea relief, and a lower healthcare provider workload. Otherwise, all our secondary endpoints are based on the hypothesis that HFNO is better than usual care.

If the study intervention failed to demonstrate non-inferiority

A careful analysis of the reasons for failure to show non-inferiority in 28-day mortality will be required before concluding that HFNO is potentially inferior. For instance, comparison with the FLORALI trial will be required.

No specific harms associated with HFNO are expected, as the preliminary data show either benefits [significant decrease in intubation rate and even increase in survival] or neither benefits nor harms.

14. Practical aspects: randomisation

Randomisation will be achieved using an electronic system incorporated in the eCRF and R software [http://www.R-project.org/]. The impact of the intervention will be assessed at the patient level. The randomisation unit is the centre. Randomisation will be centralised on a web site to ensure allocation concealment at the trial statistical centre.

Patients will be randomised into two parallel groups, in a 1:1 ratio.

Randomisation will be stratified on two factors: hypoxaemia severity (PaO_2/FiO_2<200 or ≥200 at randomisation) and presence or absence of organ dysfunction in addition to the respiratory failure [based on the SOFA score definition]. This stratification strategy will result in eight different randomisation lists that will be pre-specified and balanced through the use of permutation blocks of fixed size that will not be disclosed to the local investigators, to ensure allocation concealment and to avoid all risk of bias in patient selection.

15. Number of patients to include in the study (sample size)

We extensively discussed the study design with study-group physicians at our meeting on July 2, 2015; opinion leaders in the field of acute respiratory failure (REVA network); and reviewers of the 2015 PHRC-N [who had commented on this point]. We also based our assumptions on results of the trials by Ferrer and Stephan.[14, 66] We agree with the PHRC reviewers that the non-inferiority design is the best option. For all stakeholders, a 9% non-inferiority margin is clinically relevant, based on one-sided confidence interval of the main outcome.

Based on the 26% overall day-28 mortality rate in the iVNIctus trial (usual-care oxygen or NIV) and a 9% non-inferiority margin, with α set at 5%, to obtain a 80% power for demonstrating non-inferiority for the primary outcome, we need 816 patients (408 in each group). Recruitment is expected to take 24 months, and 6 additional months will be required for follow-up.

16. Statistical analysis

A. Minimising biases

The most effective design technique for avoiding selection bias and allowing causal inference is randomisation, centrally performed to ensure allocation concealment. Moreover, to ensure such concealment, all the investigators will remain unaware of the size of the permutation blocks used in the generation of lists.

To ensure the absence of attrition bias, the primary analysis will be made according to the intention-to-treat principle.

To ensure non-informative right censoring, a reference date for the analysis that achieved so-called administrative censoring will be used for the analysis of time-to-failure data for all outcomes that could not be fixed like 28 day mortality.

To avoid inflating the type I error rate, baseline characteristics (at randomisation) of the two groups will be compared roughly, without formal statistical testing.

B. Type of comparisons

The main comparison based on the intention-to-treat principle will compare the intervention arm to the control arm on the full-set of randomized patients. The primary hypothesis is non inferiority of the NIV in terms of 28-day mortality (primary outcome). For all secondary outcomes, our hypothesis is that HFNO is superior over standard oxygen or NIV, with two-sided p-values for comparison tests.

Secondary and exploratory comparisons of the primary endpoint will look for treatment-by-covariate interactions according to the subsets defined above.

Finally, a per-protocol analysis will be performed (see below) as in non-inferiority designs, non-inferiority is required in both the ITT and the PP analyses.

C. Interim analyses

No interim analysis will be performed. The final analysis will be started after inclusion of the planned number of patients.

D. Pre-specification of analyses

1. Analysis sets

According to the intention-to-treat principle, the full analysis set, that is, the set of patients whose data are included in the main primary analysis, is composed of all randomised patients except those who withdraw consent, who are analysed in the arm thy were allocated to.

2. Missing values and outliers

Missing values for the main outcome measure are not expected to be observed; nevertheless, in case of occurrence, they will be handled using time-to-event methods in which each patient contributes to the estimate of failure time distribution until he/she is lost-to-follow up or withdrawn from the study using competing-risks estimates.

Missing values for predictors will be imputed using multiple imputation techniques.

3. Statistical analysis strategy

Primary outcome

The main endpoint is binary, as all patients will be followed until day 28, at which time they will be classified as alive or dead. The relative risk of hospital death in the experimental versus the control arm will be estimated to assess the effectiveness of the intervention, with 95% confidence interval. Analyses adjusted on potential confounders will be performed. Intervention-by-subsets interactions will be tested using Gail and Simon statistics. In case of significant interaction, subset analyses will be performed on each subset.

Secondary outcomes

Competing-risk endpoints (ICU-acquired events including intubation, ICU-acquired infection, time to clear pulmonary infiltrates, reintubation) will be analysed using competing-risk methods. Specifically, cumulative incidences of the event of interest will be estimated, taking into account the competition between death or discharge alive from the ICU and the event of interest, then compared using the Gray test. Adjustment for potential confounders will be based on cause-specific Cox models.

ICU length of stay will be analysed overall and in survivors and dead patients, separately. The former analysis will be based on Kaplan Meier estimate while the later on the competing-risk estimator, as described above.

Analyses of longitudinal outcomes (oxygenation, dyspnea, patient comfort) will be based on joint models, taking into account the right censoring of the data.

All statistical analyses will be performed using SAS (SAS Inc, Cary, NC, USA) and R (http://www.R-project.org/) software.

17. Ethical issues, administrative aspects, and collected data (electronic Case Report Form, eCRF)

A. Data collection

Trained data collectors (clinical research technicians, CRTs) will assess the process-of-care indicators for all patients in all ICUs, using handheld wireless electronic devices connected to a central database via a local server (CLEANWEB). Each CRT will collect data in two ICUs. The central co-ordinating office will provide all CRTs with specific data-collection training for this study. Delivery of each item of care targeted by our intervention in each patient is defined as presence of at least one process-of-care indicator and absence of contra-indications to the item of care.

Data will be encrypted to ensure confidentiality and collected once daily from Monday through Friday. On weekends and holidays, data will be collected in real time or on the following workday, depending on site resources. The co-ordinating centre will conduct an on-site visit and audit of data collection at each ICU during the trial.

Appendix 1 lists the main data to be collected for the study.

B. Investigator responsibilities

The investigators will have five main responsibilities.

a) Before starting the study in the ICU, the local investigator must inform all members of the ICU team [physicians and nurses] and referring physicians in the hospital about the study. Thus, patients and relatives will then be able to seek information from any person involved in the care of the patient.

b) The local investigator must screen all immunocompromised patients who are admitted to the ICU and who need oxygen, to determine whether the study inclusion and exclusion criteria are met. Then, the local investigator must collect written informed consent from the patient or proxy. The informed consent document is appendix 2. Eligible patients who are incompetent will be included; as soon as they regain competence, they will be asked whether they consent to continue participation in the study.

c) The local investigator and entire team must provide all patients in both groups with the best standard of care.

d) The local investigator and entire team must make every effort to ensure that the study patients receive the oxygenation device allocated by the randomisation process.

e) The local investigator must ensure that all the study data are carefully collected, ensure that the CRT can find the data needed to check for accuracy, and fill in missing data.

C. Monitoring and data quality insurance

Monitoring will be performed by the CRTs of other participating ICUs. Six items will be monitored:

- Inclusion and exclusion criteria,
- Informed consent,
- Need for oxygen,
- Type of oxygenation device used in the control-group patients (Figure 1),
- Primary endpoint, and
- Secondary endpoints.

D. Approval by the ethics committee and regulatory agencies

The project will be submitted to the *Comité de Protection des Personnes* (CPP, ethics committee) of the Pitié-Salpêtrière Hospital in Paris. It will also be submitted to the *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la santé* (advisory committee on healthcare-research data processing, CCTIRS) and the Commission Nationale de l'Informatique et des Libertés (French data protection authority, CNIL).

E. Right to access the database

The database will be handled by, and only by, Prof. Sylvie Chevret, who will be responsible for data storage, the statistical analysis, and the tables and figures for the study report. She will be in close contact with the Data Safety and Monitoring Board and with the statistical editors of the journal to which the study report will be submitted for publication.

18. Ethical and safety issues

A. *General principles*

This study will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practice [GCP] guidelines, and International Conference on Harmonisation [ICH] guidelines. The study is justified by adequate clinical and laboratory data previously published in peer-reviewed journals, as discussed in the background section of this project proposal. The study protocol will be reviewed and approved by the institutional review board of each participating centre. Written informed consent will be obtained from each patient or proxy before study inclusion.

In conformity with the ethical principles that guide clinical critical-care research, the protocol incorporates measures designed to minimise risks to participants. Reporting of serious adverse events is described below.

B. Monitoring of adverse events and complications during the ICU stay

Definitions of adverse events

a. An **adverse event** is any untoward medical event occurring during the study.

b. An **unanticipated adverse event** is any medical event whose nature, severity, or frequency is not consistent with existing information regarding the risk profile of the study procedures.

c. A **serious adverse event** is any medical event that results in death, is life threatening, requires in-patient hospitalization or prolongs existing hospitalization, creates persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect. An important medical event that may not

result in death, be life threatening, or require hospitalization may be classified as a serious adverse event when good medical judgment indicates that medical or surgical intervention is needed to prevent any of the above-listed outcomes.

d. An adverse event may be related to the study intervention if it may reasonably be regarded as possibly, probably, or clearly caused by the intervention. Alternatively, the relationship of adverse events to study interventions may be characterised as either 'unrelated' or 'unlikely related'.

e. **Unanticipated problems other than adverse events** include occurrences such as (but not limited to) accidental overdoses of study medications, deviations from study inclusion/exclusion criteria, or failure to follow criteria for patient withdrawal.

Reporting of adverse events

Adverse events should be reported only if they are determined by the principal investigator to be unanticipated; serious; or possibly, probably, or clearly caused by the study intervention [as opposed to unrelated or unlikely related to the study intervention].

a. The investigator must report to the local IRB and to the clinical coordinating centre all adverse events, other than deaths, within 5 working days of their occurrence.

b. Deaths occurring locally that are unanticipated and are possibly, probably, or clearly caused by the study intervention must be reported by the investigator to the local IRB and clinical coordinating centre within 24 hours of their occurrence.

c. The investigator must report to the local IRB and to the clinical coordinating centre all unanticipated problems other than adverse events within 5 working days of their occurrence.

The clinical coordinating centre will report all serious, unexpected, and study-related adverse events to the Data Safety and Monitoring Board, by fax or telephone, within 7 calendar days. A written report will be sent to the Data Safety and Monitoring Board within 15 calendar days and these reports will be sent to the investigators for submission to their respective IRBs. The Data Safety and Monitoring Board will also review all adverse events during scheduled interim analyses. The clinical coordinating centre will distribute the written summary of the Data Safety and Monitoring Board's periodic review of adverse events to the investigators for submission to their respective IRBs.

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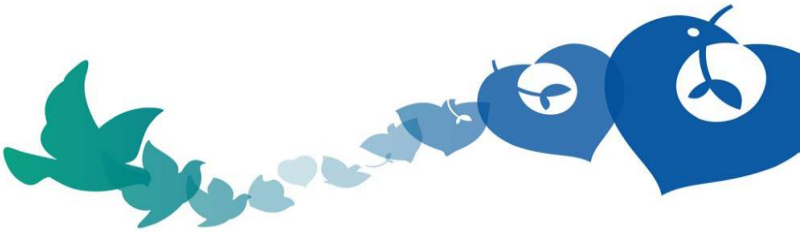
FINAL PROTOCOL (Submitted to the IRB)



Comparaison de deux modalités d'administration de l'oxygène chez les patients immunodéprimés de réanimation: oxygène à haut débit humidifié versus traitement conventionnel "HIGH"

P150912 - IDRCB N°: 2016-A00220-51

Cette recherche est organisée par l'Assistance Publique - Hôpitaux de Paris

Département de la Recherche Clinique et du Développement

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75010 Paris

NOTE D'INFORMATION – PATIENT

Madame, Monsieur,

Le Docteur…… (nom, prénom), exerçant à l'hôpital ……., vous propose de participer à une recherche biomédical intitulée : **« Comparaison de deux modalités d'administration de l'oxygène chez les patients immunodéprimés de réanimation: oxygène à haut débit humidifié versus traitement conventionnel ».** Il est important de lire attentivement cette note avant de décider si vous allez participer à cette recherche ; n'hésitez pas à demander des explications à votre médecin.

Si vous décidez de participer à cette recherche, un consentement écrit vous sera demandé.

1) Quel est le but de cette recherche?

Cette recherche porte sur la prise en charge des patients immunodéprimés admis en réanimation avec un problème respiratoire nécessitant de l'oxygène. Elle propose d'évaluer si l'utilisation de l'oxygène à haut débit humidifié est supérieure à la prise en charge habituelle (oxygène standard).

En effet, des travaux récents ont monté qu'il y avait des avantages théoriques à apporter de l'oxygène à haut débit humidifié (confort, tolérance, efficacité, prévention de l'aggravation respiratoire), mais cela n'a pas été démontré chez des patients dans votre situation.

Pour répondre à la question posée dans la recherche, il est prévu d'inclure 778 personnes présentant une insuffisance respiratoire aiguë dans des établissements de soin situés dans toute la France.

2) En quoi consiste la recherche ?

Dans la recherche proposée, nous allons évaluer si l'utilisation de l'oxygène à haut débit humidifié chez les patients immunodéprimés admis en réanimation est supérieure à la prise en charge habituelle (O_2 de faible ou moyen débit) concernant la mortalité à J28. Vous bénéficierez *par tirage au sort soit* de l'oxygène à haut débit humidifié (HFNO) *soit de la* prise en charge habituelle (O_2 de faible ou moyen débit).

3) Quel est le calendrier de la recherche ?

La recherche durera *30 mois* en tout, et votre participation sera de *6 mois*. L'étude commencera après la signature de votre consentement.

4) Quels sont les bénéfices et les contraintes liés à votre participation ?

- *Aucun bénéfice direct n'est attendu, mais* en participant à cette recherche, vous bénéficierez d'un suivi médical étroit et spécifique pour lequel aucun frais supplémentaire ne vous sera demandé. Par ailleurs, vous contribuerez à une meilleure connaissance sur le bénéfice de l'utilisation de l'oxygène à haut débit humidifié.
- *Lors de cette recherche vous aurez en plus de la prise en charge normale un prélèvement nasal par écouvillon et un prélèvement de sang (1 tube de 10 ml) pour aider à la recherche des causes de votre insuffisance respiratoire*

Si vous acceptez de participer, vous devrez respecter les points suivants :

- Informer le médecin de la recherche, de l'utilisation de tout médicament ainsi que de tout événement survenant pendant la recherche,
- Ne pas prendre part à un autre projet de recherche sans l'accord de votre médecin, ceci pour vous protéger de tout accident possible pouvant résulter par exemple d'incompatibilités possibles ou d'autres dangers,
- Etre affilié(e) à un régime de sécurité sociale ou être bénéficiaire d'un tel régime.

5) Quels sont les risques prévisibles de la recherche?

Aucun événement indésirable grave lié aux actes, procédures ou examens spécifiques de la recherche n'est attendu.

6) Quelles sont les éventuelles alternatives médicales?

La prise en charge sera identique à la normale hormis un *prélèvement nasal par écouvillon et un prélèvement de sang (1 tube de 10 ml)*. La participation à la recherche ne rajoute pas plus de contrainte.

7) Quelles sont les modalités de prise en charge médicale à la fin de votre participation?

La prise en charge à la fin de la recherche sera identique à la normale. Votre médecin pourra décider à tout moment de l'arrêt de votre participation si besoin ; il vous en expliquera les raisons.

8) Si vous participez, que vont devenir les données recueillies pour la recherche ?

Dans le cadre de la recherche biomédicale à laquelle l'AP-HP vous propose de participer, un traitement de vos données personnelles va être mis en oeuvre pour permettre d'analyser les résultats de la recherche au regard de l'objectif de cette dernière qui vous a été présenté.

A cette fin, les données médicales vous concernant *seront transmises au Promoteur de la recherche ou aux personnes ou sociétés agissant pour son compte, en France*. Ces données seront identifiées par un numéro de code et vos initiales. Ces données pourront également, dans des conditions assurant leur confidentialité, être transmises aux autorités de santé françaises.

Pour tout arrêt de participation sans retrait de consentement, les données recueillies précédemment à cet arrêt seront utilisées sauf si vous ne le souhaitez pas.

9) Comment cette recherche est-elle encadrée ?

L'AP-HP a souscrit une assurance (N° d'adhésion) garantissant sa responsabilité civile et celle de tout intervenant auprès de la compagnie HDI–GERLING par l'intermédiaire de BIOMEDICINSURE dont l'adresse est Parc d'Innovation Bretagne Sud C.P.142 56038 Vannes Cedex.

L'AP-HP a pris toutes les dispositions prévues par la loi relative à la protection des personnes se prêtant à des recherches biomédicales, loi Huriet (n° 88-1138) du 20 décembre 1988 modifiée par la loi de santé publique (n° 2004-806) du 9 août 2004.

L'AP-HP a obtenu l'avis favorable du Comité de Protection des Personnes pour cette recherche de l'hôpital Saint Louis le *[indiquer la date de la séance au format jj /mm /aaaa]* et une autorisation de l'Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM).

10) Quels sont vos droits ?

Votre participation à cette recherche est entièrement libre et volontaire. Votre décision n'entraînera aucun préjudice sur la qualité des soins et des traitements que vous êtes en droit d'attendre.

Vous pourrez tout au long de la recherche demander des explications sur le déroulement de la recherche au médecin qui vous suit.

Vous pouvez vous retirer à tout moment de la recherche sans justification, sans conséquence sur la suite de votre traitement ni la qualité des soins qui vous seront fournis et sans conséquence sur la relation avec votre médecin. A l'issue de ce retrait, vous pourrez être suivi par la même équipe médicale.

Conformément aux dispositions de la CNIL (loi relative à l'informatique, aux fichiers et aux libertés), vous disposez d'un droit d'accès et de rectification. Vous disposez également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées. Ces droits s'exercent auprès du médecin en charge de la recherche qui seul connaît votre identité. Vous pouvez également accéder directement ou par l'intermédiaire d'un médecin de votre choix à l'ensemble de vos données médicales en application des dispositions de l'article L 1111-7 du Code de la Santé Publique.

Votre dossier médical restera confidentiel et ne pourra être consulté que sous la responsabilité du médecin s'occupant de votre traitement ainsi que par les autorités de santé et par des personnes dûment mandatées par l'AP-HP pour la recherche et soumises au secret professionnel.

A l'issue de la recherche et après analyse des données relatives à cette recherche, vous pourrez être informé(e) des résultats globaux par l'intermédiaire du médecin qui vous suit dans le cadre de cette recherche.

Si vous acceptez de participer à la recherche après avoir lu toutes ces informations et discuté tous les aspects avec votre médecin, vous devrez signer et dater le formulaire de consentement éclairé se trouvant à la fin de ce document.

1237

FORMULAIRE DE CONSENTEMENT

« PATIENT »

Je soussigné(e), M^me^, M. *[rayer les mentions inutiles]* (*nom, prénom*)……...

accepte librement de participer à la recherche intitulée : « Comparaison de deux modalités d'administration de l'oxygène chez les patients immunodéprimés de réanimation: oxygène à haut débit humidifié versus traitement conventionnel » organisée par l'Assistance Publique - Hôpitaux de Paris et qui m'est proposée par le Docteur (*nom, prénom, téléphone*)……..…, médecin dans cette recherche.

- J'ai pris connaissance de la note d'information version 1.0 du 12-02-2016 de 3 *pages,* m'expliquant l'objectif de cette recherche, la façon dont elle va être réalisée et ce que ma participation va impliquer,

- je conserverai un exemplaire de la note d'information et du consentement,

- j'ai reçu des réponses adaptées à toutes mes questions,

- j'ai disposé d'un temps suffisant pour prendre ma décision,

- j'ai compris que ma participation est libre et que je pourrai interrompre ma participation à tout moment, sans encourir la moindre responsabilité et préjudice pour la qualité des soins qui me seront prodigués. J'indiquerai alors au médecin qui me suit, si je souhaite ou non que les données recueillies, jusqu'au moment de ma décision, soient utilisées,

- Je suis conscient(e) que ma participation pourra aussi être interrompue par le médecin si besoin,

- avant de participer à cette recherche, j'ai bénéficié d'un examen médical adapté à la recherche, dont les résultats m'ont été communiqués,

- j'ai compris que pour pouvoir participer à cette recherche je dois être affilié(e) à un régime de sécurité sociale ou bénéficiaire d'un tel régime. Je confirme que c'est le cas,

- j'ai bien été informé(e) que ma participation à cette recherche durera 6 mois et que cela implique que je ne pourrai pas envisager de participer à une autre recherche sans en informer le médecin qui me suit pour la recherche,

- mon consentement ne décharge en rien le médecin qui me suit dans le cadre de la recherche ni l'AP-HP de l'ensemble de leurs responsabilités et je conserve tous mes droits garantis par la loi.

Signature de la personne participant à la recherche		**Signature du médecin**	
Nom Prénom :		Nom Prénom :	
Date :	Signature :	Date :	Signature :

Ce document est à réaliser en 3 exemplaires, dont l'original doit être conservé *15 ans* par l'investigateur, le deuxième remis à la personne donnant son consentement et le troisième transmis à l'AP-HP sous enveloppe scellée à la fin de la recherche.

Original statistical plan

4. Statistical analysis strategy

Primary outcome

The main endpoint is binary, as all patients will be followed until day 28, at which time they will be classified as alive or dead. The relative risk of hospital death in the experimental versus the control arm will be estimated to assess the effectiveness of the intervention, with 95% confidence interval. Analyses adjusted on potential confounders will be performed. Intervention-by-subsets interactions will be tested using Gail and Simon statistics. In case of significant interaction, subset analyses will be performed on each subset.

Secondary outcomes

Competing-risk endpoints (ICU-acquired events including intubation, ICU-acquired infection, time to clear pulmonary infiltrates, reintubation) will be analysed using competing-risk methods. Specifically, cumulative incidences of the event of interest will be estimated, taking into account the competition between death or discharge alive from the ICU and the event of interest, then compared using the Gray test. Adjustment for potential confounders will be based on cause-specific Cox models.

ICU length of stay will be analysed overall and in survivors and dead patients, separately. The former analysis will be based on Kaplan Meier estimate while the later on the competing-risk estimator, as described above.

Analyses of longitudinal outcomes (oxygenation, dyspnea, patient comfort) will be based on joint models, taking into account the right censoring of the data.

All statistical analyses will be performed using SAS (SAS Inc, Cary, NC, USA) and R (http://www.R-project.org/) software.

Published statistical plan on TRIALS (2018) 19:157

Azoulay *et al. Trials* (2018) 19:157
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Trials

STUDY PROTOCOL Open Access

High-flow nasal oxygen vs. standard oxygen therapy in immunocompromised patients with acute respiratory failure: study protocol for a randomized controlled trial

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High-Flow Nasal Oxygen vs. Standard Oxygen Therapy in Immunocompromised Patients with Acute Respiratory Failure: Study Protocol for a Randomized Controlled Trial

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Abstract *(325 words)*

Background. Acute respiratory failure (ARF) is the leading reason for intensive care unit (ICU) admission in immunocompromised patients. High-flow nasal oxygen (HFNO) therapy is an alternative to standard oxygen. By providing warmed and humidified gas, HFNO allows the delivery of higher flow rates via nasal cannula devices, with FiO_2 values of nearly 100%. Benefits include alleviation of dyspnea and discomfort, decreased respiratory distress and decreased mortality in unselected patients with acute hypoxemic respiratory failure. However, in preliminary reports, HFNO benefits are controversial in immunocompromised patients in whom it has never been properly evaluated.

Methods and Design. This is a randomized multicenter open-label controlled superiority trial in 30 intensive care units part of the Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique (GRRR-OH). Inclusion criteria will be: 1) adults; 2) known immunosuppression; 3) ARF; 4) oxygen therapy ≥ 6L/min; 5) written informed consent from patient or proxy. Exclusion criteria will be: 1) imminent death (moribund patient); 2) no informed consent; 3) hypercapnia ($PaCO_2 \geq 50$ mmHg), 4) isolated cardiogenic pulmonary edema, 5) pregnancy or breastfeeding, 6) anatomical factors precluding insertion of a nasal cannula; 7) no coverage by the French statutory healthcare insurance system; and 8) post surgical setting from day-1 to day-6 (patients with ARF occurring after day-6 of surgery can be included).

The primary outcome measure is day-28 mortality. Secondary outcomes are intubation rate, comfort, dyspnea, respiratory rate, oxygenation, ICU length of stay, and ICU-acquired infections.

Based on an expected 30% mortality rate in the standard oxygen group, and 20% in the HFNO group, error rate set at 5% and a statistical power at 90%, 389 patients are required in

each treatment group (778 patients overall). Recruitment period is estimated at 30 months, with 28 days of additional follow-up for the last included patient.

Discussion. The HIGH study will be the largest multicenter randomized controlled trial seeking to demonstrate that survival benefits from HFNO reported in unselected patients also apply to a large immunocompromised population.

Trial registration. ClinicalTrial.gov NCT02739451, registered on April 15, 2016

Key words. Acute respiratory failure, Immunosuppression, Immunocompromised Hematology, Mortality, High flow oxygen, Oxygen, Intubation.

Background

Acute respiratory failure (ARF) is the leading reason for ICU admission of immunocompromised patients.[1-6] Mortality has decreased dramatically in this population in recent years, for several reasons. Management strategies for the underlying conditions have benefited from a number of innovations such as steroid-sparing agents, watch-and-wait approaches, and targeted therapies.[7, 8] Early ICU admission to permit the use of non-invasive diagnostic and therapeutic strategies has increased survival.[1, 9-11] Finally, the introduction of other oxygenation strategies improved the management of respiratory dysfunction (Table 1).

Oxygen therapy is the first-line treatment in hypoxemic patients. Oxygen can be delivered using low-flow devices (up to 15 L/min) such as nasal cannulas, non-rebreathing masks, and bag valve masks. The fraction of inspired oxygen (FiO_2) obtained using these devices varies with the patient's breathing pattern, peak inspiratory flow rate, delivery system, and mask characteristics. Maximum flow rates are limited in part by the inability of these devices to heat and humidify gas at high flows. Also, if the patient has a high inspiratory flow rate, the amount of entrained room air is large and dilutes the oxygen, thereby lowering the FiO_2.

Over the past two decades, devices that deliver heated and humidified oxygen at high flows through a nasal cannula were developed as an alternative to low/medium flow devices. High-flow nasal oxygen (HFNO) delivers oxygen flow rates of up to 60 L/min. An air/oxygen blender is connected via an active heated humidifier to a nasal cannula and allows FiO_2 adjustment independently from the flow rate. Compared to other devices, HFNO provides a number of physiological benefits including greater comfort and tolerance, more effective oxygenation under some circumstances and breathing pattern improvements with an increase in tidal volume and decreases in respiratory rate and dyspnea (Table 2 and Table 3). These

benefits are broadening the indications of HFNO, which has now been evaluated and used to treat hypoxemic respiratory failure, to improve oxygenation for pre-intubation, and to treat patients after surgery or after extubation (Table 4). Moreover, recent high-quality randomized controlled trials have confirmed previous preliminary results.[13, 14] Nevertheless, controlled studies in specific patient populations, such as immunocompromised patients, are needed to confirm that HFNO is clinically superior over other methods, to evaluate effects on survival, and to determine the optimal indications of HFNO compared to other modalities such as standard oxygen therapy and NIV.

Among patients with ARF, those with immunosuppression have higher mortality rates compared to unselected patients. The use of endotracheal mechanical ventilation is associated with higher mortality in immunocompromised patients. Therefore, management techniques that decrease the need for intubation may hold promise for decreasing mortality.

Four studies evaluated the feasibility and safety of HFNO in immunocompromised patients with ARF. In a retrospective single-center study reported in 2013, the feasibility of HFNO was evaluated in 45 patients with hematological malignancies.[57] Of the 45 patients, 15 recovered without intubation (33%); their hospital mortality rate was 2/15 (13%), compared to 26/30 (87%) of the patients who failed HFNO and required intubation. HFNO failure was significantly associated with bacterial pneumonia as the cause of ARF. In a single-centre study of patients with solid tumors reported in 2011, of 183 patients taken at random from the institutional database, 132 (72%) had received HFNO in the ICU to treat hypoxia.[58] Among them, 41% improved and 44% remained stable while on HFNO, whereas 15% declined. A 2013 report describes a study in 30 patients with advanced cancer and persistent dyspnea that used a randomized design to compare the physiological effects of HFNO versus BiPAP for 2 hours.[59] Both treatments similarly improved the dyspnea, as assessed using a visual analogue scale and the modified Borg scale, and non-significantly diminished the respiratory rate.

Oxygen saturation improved only with HFNO. Neither technique induced major adverse effects. The last study, published in 2015, evaluated HFNO for treating ARF requiring ICU admission in 37 lung transplant recipients.[60] HFNO proved feasible and safe and decreased the absolute risk of intubation by 29%, with a number-needed-to-treat to avoid one intubation of three. Last, in a study of 50 Do-Not-Intubate patients with hypoxemic respiratory distress, including a third of immunocompromised patients, HFNO allowed an improvement in oxygenation and decreased respiratory rate.[61],

Four studies assessed HFNO efficacy in immunocompromised patients with ARF. The first study, by Mokart et al., analyzed a retrospective cohort of 178 patients with cancer and ARF (O_2 > 9 L/min), including 76 (43%) treated with NIV+HFNO, 74 (42%) with NIV+low/medium-flow O_2, 20 (11%) with HFNO alone, and 8 with low/medium-flow O_2 alone.[62] NIV+HFNO was associated with lower mortality (37% vs. 52% in remaining patients, *p*=0.04) and was independently associated with lower day-28 survival in a propensity-score analysis. Second, in a sub-study of data from our recent iVNIctus RCT of early NIV in immunocompromised patients with ARF,[63] 141/374 (38%) patients received HFNO, and either NIV or low/medium-flow oxygen was used in the other patients. To allow accurate adjustment, we built a propensity score using variables available at ICU admission. Intubation rate and day-28 mortality were not significantly different in the HFNO arm compared to the NIV or low/medium-flow oxygen arm. Third, in 115 immunocompromised patients with ARF, 60 (52 %) were treated with HFN0 alone and 55 (48 %) with NIV as first-line therapy with 30 patients (55 %) receiving HFNO and 25 patients (45 %) standard oxygen between NIV sessions[66]. The rates of intubation and 28-day mortality were higher in patients treated with NIV than with HFNO (55 vs. 35 %, p = 0.04, and 40 vs. 20 %, p = 0.02, respectively). Using propensity score-matched analysis, NIV was associated with mortality. Using multivariate analysis, NIV was independently associated with intubation and mortality.

Last, in a post-hoc analysis of the FLORALI study that only included immunocompromised patients, 8 (31%) of 26 HFNO patients, 13 (43%) of 30 patients treated with standard oxygen, and 17 (65%) of 26 patients treated with NIV required intubation at 28 days (p=0·04). Odds ratios for intubation did not differ however between HFNO patients and those receiving standard oxygen only[67]. Last, in the Efraim study that included 1611 immunocompromized patients with acute respiratory failure, the use of HFNO had an effect on intubation rate but not on mortality, whereas, failure to identify ARF etiology was associated with increased intubation rate and mortality[68].

Although the effects of HFNO have varied across studies, the data establish that this treatment modality is feasible and safe in immunocompromised patients. They also demonstrate that outcomes with HFNO are at least as good as with other oxygen therapy methods in this population. Thus, they warrant further trials to determine whether HFNO improves survival in unselected immunocompromised patients with hypoxemic ARF. Immunocompromised patients have specific treatment needs, as shown by their 2-fold higher mortality rate after intubation compared to other patients. Data on HFNO in immunocompromised patients are conflicting.

We therefore designed the present RCT (HIGH). This RCT is a superiority study of HFNO versus other oxygenation strategies (low/medium-flow oxygen) in immunocompromised patients requiring oxygen. The primary endpoint is day-28 survival. The patients will be recruited at 31 centers belonging to the GRRR-OH, a research network that specializes in the management of critically ill immunocompromised patients and has a particularly high level of expertise in respiratory care strategies. The control group will receive low/medium-flow oxygen as deemed appropriate by the physician, since the recent large iVNIctus trial by our group did not show any superiority of NIV on intubation rates or survival. The experimental group will receive continuous HFNO at any time after ICU

admission, for pre-oxygenation before intubation, after extubation, and for any ICU procedure that might induce hypoxemia). HFNO will not be used in the control group.

Methods / Design

Design and settings

The HIGH trial is a prospective, multicenter, open-label, randomized controlled trial comparing HFNO versus other oxygenation strategies (low/medium-flow oxygen) in immunocompromised patients requiring oxygen. The study hypothesis is that early HFNO decreases mortality on day 28 after randomization in immunocompromised patients requiring ICU admission for ARF.

Ethical aspects

The study was approved by the local independent ethic committee (Comite de Protection des Personnes CPP Ile de France IV, Saint Louis on March 28, 2016, number 2016/08), the French health authorities (AFSSAPS) on March 14, 2016, number EudraCT 2016-A00220-51. The University Hospital of Paris (AP-HP) and by delegation the Clinical Research and Development Department (DRCD) is the sponsor of the trial (Sponsor code: P150912/IDRCB No: 2016-A00220-51). Informed consent will be obtained from each participant.

Participating intensive care units

All participating centers belong to the Grrr-OH, a research network specializing in the respiratory care of critically ill immunocompromised patients. All these centers have previously taken part in observational studies, surveys, or therapeutic trials. They all have high case-volumes of patients with immune deficiencies due to immunosuppressive drugs, solid-organ transplantation, malignancies, or systemic diseases. Although they are specialized in oncology and hematology, they also admit high volumes of patients with systemic diseases, solid organ transplant and other immunosuppression.

Study population

Eligible patients are immunocompromised patients who are admitted to the ICU and need oxygen supplementation (of at least 6l/min) at any stage of their ICU stay. All randomized patients will be included in the full set of analysis (intent-to-treat basis).

To be randomized patients should fulfill all the following inclusion criteria 1) adult (age ≥18 years); 2) known immunosuppression defined as one or more of the following: immunosuppressive drugs/long-term [>3 months] or high-dose [>0.5 mg/kg/day] steroids, solid organ transplant, solid tumor having required cancer care in the last 5 years, hematological malignancy or primary immune deficiency; 3) ICU admission for Acute Respiratory Failure, 4) need for oxygen therapy ≥6L/min, 5) Written informed consent from the patient or proxy (if present) before inclusion or once possible when patient has been included in a context of emergency.

Exclusion criteria were: 1) imminent death (moribund patients); 2) refusal of study participation or to pursue the study by the patient; 3) hypercapnia with a formal indication for NIV ($PaCO_2 \geq 50$ mmHg, formal indication for NIV); 4) isolated cardiogenic pulmonary edema (formal indication for NIV). Patients with pulmonary edema associated with another ARF etiology can be included; 5) pregnancy or breastfeeding; 6) anatomical factors precluding the use of a nasal cannula; 7) absence of coverage by the French statutory healthcare insurance system; 8) post-surgical setting from D1 to D6 (patients with ARF occurring after day-6 of surgery can be included).

Randomization

Randomization will be stratified on three factors, measured at study inclusion, namely: 1) time since ICU admission, segregating D0 (calendar date of ICU admission), D1, D2

versus ≥ D3; 2) hypoxemia severity, segregating oxygen flow < vs. ≥ 9L to reach SpO_2≥ 95% at randomization; 3) shock, based on the administration of catecholamine. Thus, analysis could consider treatment-by-subset interaction on such strata.

Randomization will be achieved using an electronic system incorporated in the eCRF and R software [http://www.R-project.org/]. The impact of the intervention will be assessed at the patient level. The randomization unit is the center. Randomization will be centralized on a web site to ensure allocation concealment at the trial statistical center. Patients will be randomized into two parallel groups, in a 1:1 ratio. Randomization will be stratified (see above), resulting in eight different randomization lists that will be pre-specified and balanced through the use of permutation blocks of fixed size that will not be disclosed to the local investigators, to ensure allocation concealment and to avoid all risk of bias in patient selection.

Study interventions

This open randomized controlled trial will compare two oxygenation strategies.

A. Standard oxygen as the usual care [control group]

Patients in the control group will receive the best standard of care, according to the usual practice of the local intensivists and primary-care physicians. Oxygen therapy will be delivered using any device or combination of devices that are part of usual care: nasal oxygen, and mask with or without a reservoir bag and with or without the Venturi system. Oxygen settings are set to target a SpO_2≥95. HFNO will not be used in the control group. NIV will not be used at all in this trial, unless patients develop hypercapnia or pulmonary edema throughout the ICU stay, for the time they meet these conditions. ICU discharge will be allowed when patients will meet the ability to maintain SpO_2≥95% with less than 6 L/min oxygen.

B. High-flow nasal oxygen [intervention group]

Patients in the HFNO group will receive the best standard of care, according to the usual practice of the local intensivists and primary physicians, with one exception: supplemental oxygen will be provided only by continuous HFNO. HFNO will be initiated at a flow rate of 50 L/min and 100% FiO_2. If the target SpO_2 is not reached, the flow rate will be increased to 60 L/min. Then, FiO_2 will be tapered to target a $SpO_2 \geq 95\%$. The minimal flow rate within the first three days will be 50 L/min. In patients who require intubation, HFNO will be used during laryngoscopy and immediately after extubation. Also, HFNO will be used before, during, and after all ICU procedures. Patients with discomfort due to HFNO will have their flow rate decreased until the discomfort resolves. If the nasal prongs generate significant discomfort or skin breakdown, a Venturi mask will be used instead until HFNO can be used again; except in this situation, standard oxygen will be used in the intervention group. NIV will however be used in the same conditions than in the control group.

HFNO will be stopped based on clinical criteria [improvement of clinical signs of respiratory distress], $PaO_2/FiO_2 > 300$, and ability to maintain $SpO_2 \geq 95\%$ with less than 6 L/min of standard oxygen [allowing ICU discharge as HFNO may not be available in the wards].

Data collection and follow-up

Evaluation at study inclusion (T0)

The evaluation at study inclusion will include patient's characteristics, underlying disease, associated organ dysfunction, investigations usually performed at ICU admission in immunocompromised patients with ARF, and ARF etiology.

Evaluations throughout study participation

Evaluations performed throughout study participation will include physiological variables including respiratory and ventilation parameters (respiratory rate, SpO_2, oxygen flow and/or FiO_2), blood gases and Chest X-Ray (the worst values will be recorded). Results of investigations, ICU-acquired infections and data on oxygenation tolerance and efficacy as well as on comfort will be also collected.

ICU-acquired infections are defined as any new-onset infection starting more than 48 hours after ICU admission for which the clinical team started a new antibiotic regimen. Every single infection will be made using Centers for Disease Control and Prevention definitions.[69]

Evaluation at the end of study participation

Evaluations performed at the end of study participation will consist of mortality on day 28, need for intubation, ICU and hospital lengths of stay and ICU-acquired infections. All elements allowing to record secondary endpoints will be collected.

Organization of the trial

Funding and support

The HIGH trial is promoted by the Assistance Publique - Hôpitaux de Paris and supported by a grant from the French Ministry of Health (Programme Hospitalier de Recherche Clinique 2012; AOM12456).

Coordination and implementation of the trial

Each medical and paramedical team in the 31 participating ICUs were trained in the protocol and data collection using an electronic case-record form during formal meetings prior to screening and inclusion. The electronic case-record form was developed with CleanWEBTM, a centralized, secure, interactive, web-response system accessible from each study center, provided and managed by Telemedicine Technologies.

Local physicians and clinical research assistants in each participating ICU are responsible for daily screening and inclusion of patients, compliance with protocol, availability of data requested for the trial and completion of the electronic case-record form. In accordance with French law, the electronic case-record form and database were validated by appropriate committees (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé; Commission Nationale de l'Informatique et des Libertés).

Interim analysis

One interim analysis by an independent data safety and monitoring board is planned after the occurrence of 100 deaths. The data safety and monitoring board will be blinded to allocation of groups and may decide premature termination of the study. The board consists of one methodologist, one pulmonologist, and one intensivist. Data are blindly analyzed but unblinding is possible on request of the data safety and monitoring board. An extraordinary meeting may be requested by the principal investigator or the methodologist, in the case of unexpected events that might affect continuation of the protocol.

Blinding

Given the nature of the interventions, physicians, nurses, and patients cannot be blinded for the randomized interventions. The analysis will be blinded to allocation of groups.

Study outcomes

Primary endpoint

The primary endpoint of this trial is day-28 mortality.

Secondary endpoints

The secondary endpoints are: intubation rate (proportion of patients requiring invasive mechanical ventilation) on day 28, patient comfort (visual analogue scale [VAS]), dyspnea (VAS and Borg scale), respiratory rate, oxygenation (based on the lowest SpO_2 value and on PaO_2/FiO_2 from day 1 to day 3, ICU stay length, incidence of ICU-acquired infections.

Statistical methods

All statistical analyses will be performed using SAS (SAS Inc, Cary, NC, USA) and R (http://www.R-project.org/) software.

Sample size calculation

Based on a 30% day-28 mortality rate in usual-care oxygen group, and a 20% day-28 mortality rate in the HFNO group, with α set at 5%, to obtain a 90% power for demonstrating superiority for the primary outcome, we need 778 patients (389 in each group).

Recruitment is expected to take 30 months, and 28 additional days will be required for follow-up.

Interim analyses

One interim analysis will be performed, once 100 deaths will have been observed. Due to inflation of type I error consideration, it will use the Haybittle-Peto boundary, that is a p-value threshold of 0.001 for the interim analysis (while the terminal analysis will use a threshold of 0.05, as scheduled) in the sample size computation). Moreover, to get insight in the difference across arms in terms of futility or efficacy, the Bayesian posterior probability of the 28 day mortality rate and of the log odds ratio will be computed, using a uniform non informative prior. The final analysis will be started after inclusion of the planned number of patients.

Methodology of the statistical analysis

The main comparison based on the intention-to-treat principle will compare the intervention arm to the control arm on the full-set of randomized patients. The primary hypothesis is superiority of the NIV in terms of 28-day mortality (primary outcome). For all secondary outcomes, our hypothesis is that HFNO is superior over standard oxygen, with two-sided p-values for comparison tests. Secondary and exploratory comparisons of the primary endpoint will look for treatment-by-covariate interactions according to the subsets defined above. Finally, a per-protocol analysis will be performed.

Missing values and outliers

Missing values for the main outcome measure are not expected to be observed; nevertheless, in case of occurrence, they will be handled using time-to-event methods in which each patient contributes to the estimate of failure time distribution until he/she is lost-to-follow up or withdrawn from the study using competing-risks estimates. Missing values for predictors will be imputed using multiple imputation techniques.

Analysis of the primary outcome

The main endpoint is binary, as all patients will be followed until day 28, at which time they will be classified as alive or dead. The relative risk of hospital death in the experimental versus the control arm will be estimated to assess the effectiveness of the intervention, with 95% confidence interval. Analyses adjusted on potential confounders will be performed. Intervention-by-subsets interactions will be tested using Gail and Simon statistics. In case of significant interaction, subset analyses will be performed on each subset.

Analysis of the secondary outcomes

Competing-risk endpoints (ICU-acquired events including intubation, ICU-acquired infection) will be analysed using competing-risk methods. Specifically, cumulative incidences of the event of interest will be estimated, taking into account the competition between death or discharge alive from the ICU and the event of interest, then compared using the Gray test. Adjustment for potential confounders will be based on cause-specific Cox models. ICU length of stay will be analysed overall and in survivors and dead patients, separately. The former analysis will be based on Kaplan Meier estimate while the later on the competing-risk estimator, as described above. Analyses of longitudinal outcomes (oxygenation, dyspnea, patient's comfort) will be based on joint models, taking into account the right censoring of the data.

Discussion

ARF remains the most frequent and challenging life-threatening event in patients with hematological malignancies. In patients with prolonged neutropenia (acute leukemia or bone marrow transplant recipients), respiratory events occur in up to half of cases, of which a further half are complicated by ARF. Despite a recent improvement in survival, intubation and subsequent invasive mechanical ventilation remains associated with high mortality in immunocompromised patients with ARF. In recent studies, mortality after intubation was 60% in hematological patients and 40% in immunocompromised patients. In that setting, any strategy that could prevent intubation and subsequent increase in mortality could be of benefit.

HFNO has been associated with an increase survival for immunocompetent patients managed in the ICU for a hypoxemic ARF, and with a decrease in intubation rate in the most hypoxemic patients. Nevertheless, data are scarce in specific patient populations, such as immunocompromised patients, who are at high risk of intubation when presenting with ARF. Clearly, data are needed to confirm that HFNO is clinically superior over other methods in immunocompromised patients. It fully justifies the HIGH trial.

As a consequence of the negative result of our recent iVNIctus multicentre randomized controlled trial that did not show a benefit of NIV on mortality nor on intubation in immunocompromised patients with ARF, we have decided that NIV would not delivered in a systematic way to the patients included in the HIGH trial. In addition, recent data from an ancillary study of the FLORALI trial suggests that intubation rate and mortality were higher in patients treated with NIV than in those treated with HFNO. However, clinicians in charge will be allowed to deliver NIV to patients with a well-established indication of NIV, such as cardiogenic pulmonary edema and hypercapnic ARF.

We expect the HIGH trial to assess an oxygenation management strategy including HFNO. We hypothesize that mortality will be lower in patient receiving HFNO, possibly in association with a reduction of the intubation rate. We also expect the HIGH trial to analyze the factors that predict intubation in immunocompromised patients with ARF.

Trial status

Enrollment is ongoing, having started on May 2016. The first interim analysis was conducted in March 13, 2017, and the data safety and monitoring board recommended that the study be continued. On November 13, 2017, 686 patients were included in the trial. Enrollment is expected to be completed in February 2018.

Abbreviations

HFNO: high flow nasal oxygen

ICU: intensive care unit

NIV: noninvasive ventilation

ARF : acute rspiratory failure

GRRR-OH : Groupe de recherche respiratoire en réanimation oncohématologique

Declarations

- Ethical Approval and Consent to participate

The study was approved by the IRB of the St-Louis hospital. All patients or relatives provided signed informed consent.

- Consent for publication

All authors consent to see this protocol article published. All have given input on the submitted version and approved it.

- Availability of supporting data

All the data collected for this study are in the hands of Sylvie Chevret MD, PhD who is the methodologist of the trial and statistician for the study. All data will be available upon request.

- Competing interests

None of the authors has any conflict of interest in relation with this study. The institutions of Elie Azoulay, Samir Jaber, Alexandre Demoule and Virginie Lemiale have received scientific support from Fisher & Payckle outside this study.

- Funding

The study has received a grant from the French Ministry of Health.

- Authors' contributions

EA, VL, DM and AD have drafted the initial version of the protocol and have requested funding to the Ministry of health. SC has designed the study and planned the statistics. She also run the interim analyses. SN, LA, FP, LK and FB participated to study conception and to address initial discussions that helped obtain the grant. EA, VL, DM, AD, SN, LA, FP, LK FB. KK, FB, JR, AS, GL, JMC, JM, FW, AK, VP, PP, CG, SJ, JO, MY, NT, LB, CL, AL, NB, JHR, LP, AR and MD also gave feedback on study design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript. All authors attended the investigators meeting, are responsible for all decisions regarding the study, are responsible for recruiting patients, collecting data and completing information on e-crf.

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2082 **Table 1: Definitions for oxygen delivery devices and reported outcomes using HFNO**

Definitions	
HFNO	Device that delivers humidified and warmed high-flow oxygen at flows greater than 15 L/min.
Usual oxygen therapy devices	Devices used to treat spontaneously ventilating patients in the ICU who require supplemental oxygen. They deliver either - low-flow oxygen [including nasal cannula, Ventimask® without Venturi effect, and non-rebreather mask] - or medium-flow oxygen [Venturi masks and medium-flow facemasks]
Non-invasive ventilation (NIV)	Administration of ventilatory support without using an endotracheal tube or tracheostomy tube. Ventilatory support can be provided through diverse interfaces (mouthpiece, nasal mask, facemask, or helmet), using a variety of ventilatory modes (e.g., volume ventilation, pressure support, bi-level positive airway pressure [BiPAP; see the image below], proportional-assist ventilation [PAV], and continuous positive airway pressure [CPAP]) with either dedicated NIV ventilators or ventilators also capable of providing support through an endotracheal tube or mask
Clinical outcomes in HFNO	**Assessed by measuring**
Oxygenation	Continuous SpO_2

[desaturation]	PaO_2 at fixed times PaO_2/FiO_2 ratio
Ventilation	$PaCO_2$
Airway pressures	Nasopharyngeal or hypopharyngeal catheter
Work of breathing	Respiratory rate
Patient comfort and adherence	Visual analogue scale [VAS] for breathing difficulties Satisfaction and tolerance; Global comfort Dyspnoea [VAS or Borg scale], dry mouth
Cardiovascular status	Heart rate Shock; Need for vasopressors
Complications	Need for NIV Need for intubation and mechanical ventilation [MV]; Mortality

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Table 2: Drawbacks of standard oxygen therapy that limit the effectiveness and tolerance of oxygen delivery

Oxygen is not humidified at low flow - **dry nose** - **dry throat** - **dry mouth** - **nasal pain** - **ocular irritation,** - **nasal and ocular trauma** - **discomfort related to the mask** - **gastric distension** - **aspiration** - **global discomfort**
Insufficient heating leads to poor tolerance of oxygen therapy
Unwarmed and dry gas may cause bronchoconstriction and may decrease pulmonary compliance and conductance.
With low/medium-flow devices, oxygen cannot be delivered at flows greater than 15 L/min, whereas inspiratory flow in patients with respiratory failure varies widely and is considerably higher, between 30 and more than 100 L/min.
Given the difference between the patient's inspiratory flow and the delivered flow, FiO_2 is both variable and often lower than needed.

Table 3: Physiological benefits of HFNO compared to conventional oxygen therapy

FiO_2 values are higher and more stable **because the delivered flow rate is higher than the spontaneous inspiratory demand and because the difference between the delivered flow rate and the patient's inspiratory flow rate is smaller.** ☞ **The flow rate must be set to match the patient's inspiratory demand and/or the severity of the respiratory distress.**
The anatomical dead space is decreased, via washout of the nasopharyngeal space **Consequently, a larger fraction of the minute ventilation reaches the alveoli, where it can participate in gas exchange.** **Respiratory efforts become more efficient.** **Thoraco-abdominal synchrony improves.**
The work of breathing is decreased **because HFNO mechanically stents the airway,** **provides flow rates that match the patient's inspiratory flow, and markedly attenuates the inspiratory resistance associated with the nasopharynx, thereby eliminating the attendant work of breathing.**
The gas delivered is heated and humidified

Warm humid gas reduces the work of breathing and improves muco-ciliary function, thereby facilitating secretion clearance, decreasing the risk of atelectasis, and improving the ventilation/perfusion ratio and oxygenation.

The body is spared the energy cost of warming and humidifying the inspired gas.

Warm humid gas is associated with better conductance and pulmonary compliance compared to dry, cooler gas.

☞ **HFNO delivers adequately warmed and humidified gas only when the flow rate is >40 L/min.**

Positive airway pressures are increased

The nasal cannula generates continuous positive pressures in the pharynx of up to 8 cm H_2O.

The positive pressure distends the lungs, ensuring lung recruitment and decreasing the ventilation-perfusion mismatch in the lungs.

End-expiratory lung volume is greater with HFNO than with low-flow oxygen therapy.

☞ **Minimising leaks around the cannula prongs is of the utmost importance.**

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2093 **Table 4: Clinical studies on HFNO therapy in adults with hypoxemic acute**

2094 **respiratory failure (ARF)**

Reference	Study design	Population	N patients	Results
Hypoxemic acute respiratory failure in the ICU				
22	Cohort, unselected patients. HFNO 50 L/min vs. face mask oxygen	Hypoxaemic ARF	38	Improved oxyge Decreased respir
23	Cohort, unselected patients. HFNO 20-30 L/min vs. face mask oxygen	Hypoxaemic ARF	20	Improved oxyge Decreases in resp distress, and thoraco
47	HFNO compared to face mask oxygen	Hypoxaemic ARF	60	Decreased treatm 30% to 10%. Fewer
48	Cohort study, HFNO 20-30 L/min vs. face mask oxygen	Hypoxaemic ARF	20	Improved comfo
49	Cohort study (post hoc)	Hypoxaemic ARF (2009 A/H1N1v outbreak)	20	9/20 (45%) succ vasopressors require hours of HFNO, non and needed higher o

43	Observational, single-centre study	ARDS	45	40% intubation r SAPSII, developmen toward lower PaO_2/F
13	Multicentre, open-label RCT with 3 groups: HFNO, usual oxygen therapy (face mask), or non-invasive positive-pressure ventilation.	Hypoxaemic ARF, $PaO_2/FiO_2 \leq 300$	310	Intubation rate w oxygen, and 50% wi days by day 28 was s Decreased D-90 mor
50	Retrospective before/after study of HFNO	Hypoxaemic ARF	172	Reduced need fo decreased ventilator-
42	Patients intubated after HFNO	Hypoxaemic ARF	175	In patients intuba %), higher extubatio ventilator-free days. decreased ICU morta
Hypoxemic acute respiratory failure in the ED				
51	Patients with ARF (>9 L/min oxygen or clinical signs of respiratory distress)	Hypoxaemic ARF	17	Decreased dyspn oxygenation
52	RCT of HFNO vs. standard oxygen for 1 h	Hypoxaemic ARF	40	Decreased dyspn

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