EDITORIAL

High-Flow Nasal Oxygen—The Pendulum Continues to Swing in the Assessment of Critical Care Technology

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Standard oxygen by mask or nasal prongs has been the first-line therapy for patients with acute hypoxemic respiratory failure (AHRF), followed by intubation to provide invasive mechanical ventilation for patients for whom this approach has failed. Although intubation and subsequent invasive mechanical ventilation can be lifesaving, these procedures are associated with many complications[1] and some patients with comorbidities—for example, those who are immunosuppressed—have disproportionately high morbidity and mortality.[2] Two technologies have been developed to bridge the therapy gap between standard oxygen therapy and invasive mechanical ventilation: noninvasive ventilation (NIV) and high-flow nasal oxygen therapy. Although there is controversy about how these technologies fit in the management of AHRF, they share a similar proliferation based on early enthusiasm followed by widespread adoption and over time a tempering of expectations related to ongoing evaluation in randomized clinical trials.

Related article

Although NIV was first introduced in the 1940s, its popularity for the care of immunosuppressed patients with AHRF increased when initial clinical trials reported substantial improvements in mortality and a reduction in rates of endotracheal intubation.[3,4] These data and an observational study of 1302 immunosuppressed patients were the basis for a conditional recommendation for the use of NIV in immunocompromised patients with AHRF before intubation in the current European Respiratory Society/American Thoracic Society guidelines.[5] However, a recent multicenter, randomized trial by Lemiale et al[6] of 374 immunosuppressed patients showed that early NIV compared with standard oxygen therapy was not associated with clinical benefits. In addition, a post hoc analysis of the FLORALI trial, comparing high-flow nasal oxygen therapy with NIV and standard oxygen therapy in AHRF, suggested that NIV might be associated with an increased risk of intubation and mortality in this subgroup of patients with AHRF.[7]

Given the pendulum swing in optimism for NIV, could there be a role for high-flow nasal oxygen therapy in immunocompromised patients? This technology has been widely adopted, and its popularity has been driven by early positive studies, the improvement in physiologic parameters seen during its use (particularly an increase in the ratio of Pao_2 to fraction of inspired oxygen [Fio_2]), and a general ease of application.[8,9] However, robust studies clarifying the niche this technology best serves have been lacking, especially in the immunosuppressed patient population.

In this issue of *JAMA*, Azoulay and colleagues[10] address this question. In this multicenter trial, the authors recruited 776 immunosuppressed patients with AHRF and randomized them to receive high-flow nasal oxygen therapy vs standard oxygen therapy. Based on their calculated Pao_2:Fio_2 ratio both at and 6 hours after randomization and the high mortality in both the intervention and the control groups, the population studied was appropriate in regard to degree of hypoxemia and severity of illness to warrant consideration of innovative therapies beyond routine initial oxygen therapy to improve outcome. However, no significant benefit from use of high-flow oxygen therapy was seen. Intubation rates were similar in both groups, 150 of 388 (38.7%) with high-flow oxygen therapy and 170 of 388 (43.8%) with standard oxygen therapy. Similarly, 28-day mortality was not significantly different between groups—138 of 388 (35.6%) with high-flow oxygen therapy and 140 of 388 (36.1%) with standard oxygen therapy.

There may have been some adverse effects of high-flow nasal oxygen therapy in the trial. The authors point out that patients who received high-flow oxygen therapy had a longer intensive care unit (ICU) stay when compared with patients receiving standard oxygen therapy (8 days vs 6 days), although the difference was not statistically significant ($P = .07$). This observation is common in clinical practice, whereby patients with AHRF who receive high-flow oxygen therapy are considered to need a high-maintenance, high-cost admission to an ICU until they can be transitioned to standard oxygen therapy. Furthermore, because there are no precise guidelines for weaning from high-flow therapy, its use may lead to increased and perhaps unnecessary use of hospital and critical care resources.

The medical community's craving for innovation often fuels overzealous enthusiasm for positive results of interventions in preliminary studies that are subsequently contradicted when larger, multicenter trials are undertaken.[11] One reason for early enthusiasm is that physicians do not want to withhold potentially beneficial therapies from patients. This is especially true in critical care when the intervention is perceived to have a pathophysiologic rationale. However, once a technology has been adopted, it is difficult to de-adopt, even if later, more robust evidence suggests that its continued use is unjustified.[16] Even when trials have negative results, researchers and clinicians often seek to find subgroups that may have some benefit (such as with trials of colloids in shock or of activated protein C in severe sepsis) so that innovation is not wasted. However, if therapies are posited to have a role in important subgroups, it is important that such a role be demonstrated with adequate rigor in prospective clinical trials.[12,13]

It is conceivable that one reason there has been such an embrace of high-flow nasal oxygen therapy is publication bias. Researchers may not submit their negative studies because they perceive their results are uninteresting, or journal priorities and the agenda of funding groups may influence the dissemination of information from completed clinical trials by limiting publication.[14] However, trials that fail to demonstrate positive effects of new technologies or therapies often have clinical utility. The trial by Azoulay et al, despite its negative findings, helps clarify the application of high-flow oxygen therapy in the immunosuppressed patient population. It is important to publish high-quality, negative randomized clinical trials to prevent excessive application of therapies that are not beneficial and, once popularized, may take years to find their proper application.

Given the available evidence, the important clinical question is in which patients with AHRF should high-flow nasal oxygen therapy be used? Based on the post hoc subgroup analysis in the FLORALI trial, high-flow oxygen therapy used in patients with severe hypoxemia (Pao_2:FIO_2 ratio ≤200 mm Hg) was associated with a reduced rate of intubation, which likely drove the mortality benefit of high-flow oxygen therapy compared with NIV and standard oxygen therapy.[15] However, the patients in the current study by Azoulay et al had severely impaired oxygenation yet did not benefit. Thus, based on current information, high-flow oxygen therapy should not be considered a preferred therapy for immunosuppressed patients with AHRF, and additional studies including assessment of other technologies to avoid invasive ventilation are clearly needed.

ARTICLE INFORMATION

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Effect of High-Flow Nasal Oxygen vs Standard Oxygen on 28-Day Mortality in Immunocompromised Patients With Acute Respiratory Failure

The HIGH Randomized Clinical Trial

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IMPORTANCE High-flow nasal oxygen therapy is increasingly used for acute hypoxemic respiratory failure (AHRF).

OBJECTIVE To determine whether high-flow oxygen therapy decreases mortality among immunocompromised patients with AHRF compared with standard oxygen therapy.

DESIGN, SETTING, AND PARTICIPANTS The HIGH randomized clinical trial enrolled 776 adult immunocompromised patients with AHRF (Pao_2 <60 mm Hg or Spo_2 <90% on room air, or tachypnea >30/min or labored breathing or respiratory distress, and need for oxygen ≥6 L/min) at 32 intensive care units (ICUs) in France between May 19, 2016, and December 31, 2017.

INTERVENTIONS Patients were randomized 1:1 to continuous high-flow oxygen therapy (n = 388) or to standard oxygen therapy (n = 388).

MAIN OUTCOMES AND MEASURES The primary outcome was day-28 mortality. Secondary outcomes included intubation and mechanical ventilation by day 28, Pao_2:Fio_2 ratio over the 3 days after intubation, respiratory rate, ICU and hospital lengths of stay, ICU-acquired infections, and patient comfort and dyspnea.

RESULTS Of 778 randomized patients (median age, 64 [IQR, 54-71] years; 259 [33.3%] women), 776 (99.7%) completed the trial. At randomization, median respiratory rate was 33/min (IQR, 28-39) vs 32 (IQR, 27-38) and Pao_2:Fio_2 was 136 (IQR, 96-187) vs 128 (IQR, 92-164) in the intervention and control groups, respectively. Median SOFA score was 6 (IQR, 4-8) in both groups. Mortality on day 28 was not significantly different between groups (35.6% vs 36.1%; difference, −0.5% [95% CI, −7.3% to +6.3%]; hazard ratio, 0.98 [95% CI, 0.77 to 1.24]; *P* = .94). Intubation rate was not significantly different between groups (38.7% vs 43.8%; difference, −5.1% [95% CI, −12.3% to +2.0%]). Compared with controls, patients randomized to high-flow oxygen therapy had a higher Pao_2:Fio_2 (150 vs 119; difference, 19.5 [95% CI, 4.4 to 34.6]) and lower respiratory rate after 6 hours (25/min vs 26/min; difference, −1.8/min [95% CI, −3.2 to −0.2]). No significant difference was observed in ICU length of stay (8 vs 6 days; difference, 0.6 [95% CI, −1.0 to +2.2]), ICU-acquired infections (10.0% vs 10.6%; difference, −0.6% [95% CI, −4.6 to +4.1]), hospital length of stay (24 vs 27 days; difference, −2 days [95% CI, −7.3 to +3.3]), or patient comfort and dyspnea scores.

CONCLUSIONS AND RELEVANCE Among critically ill immunocompromised patients with acute respiratory failure, high-flow oxygen therapy did not significantly decrease day-28 mortality compared with standard oxygen therapy.

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Supplemental content

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Survival with immune deficiencies is increasingly common,[1] owing to the increasing life expectancy after cancer[2] and expanding use of transplantation[3] and immunosuppressant drugs.[4] In immunocompromised patients, intensive treatments improve survival[2] but only at the cost of life-threatening events, chiefly affecting the lungs.[5] Acute hypoxemic respiratory failure (AHRF) in immunocompromised patients, the first reason for intensive care unit (ICU) admission,[6,7] is still associated with high mortality rates.[5] Need for invasive mechanical ventilation (IMV) is a key prognostic factor in immunocompromised patients, and avoiding IMV has become a major treatment goal. However, no survival benefit of noninvasive ventilation (NIV) compared with standard oxygen therapy was reported from a multicenter randomized clinical trial (RCT),[8] in contrast to an earlier single-center study.[9]

High-flow nasal oxygen therapy, which delivers warm and humidified oxygen through a nasal cannula, has shown conflicting results regarding its benefit over standard oxygen therapy in RCTs. Although high-flow oxygen therapy significantly increased the number of ventilator-free days and decreased day-90 mortality in patients with AHRF,[10] this was not confirmed in immunocompromised patients, based on 2 post hoc analyses of RCTs.[11,12] Moreover, high-flow oxygen therapy failed to improve comfort, dyspnea, or thirst compared with a Venturi mask in a pilot multicenter RCT.[13] Thus, uncertainty remains about whether benefits can be expected from high-flow oxygen therapy in immunocompromised patients with AHRF.

The HIGH multicenter RCT was designed to test the hypothesis that high-flow oxygen therapy, compared with standard oxygen therapy, decreases all-cause day-28 mortality in critically ill immunocompromised patients with AHRF.[14]

Key Points

Question In immunocompromised patients with acute hypoxemic respiratory failure, is high-flow nasal oxygen therapy superior to standard oxygen therapy with respect to mortality at day 28?

Findings In this randomized clinical trial that included 776 critically ill immunocompromised patients receiving at least 6 L/min of oxygen, high-flow oxygen therapy compared with standard oxygen therapy did not significantly reduce day-28 mortality (35.6% vs 36.1%, respectively).

Meaning Among immunocompromised patients with acute respiratory failure, high-flow oxygen therapy did not significantly reduce mortality compared with standard oxygen therapy.

Methods

Study Design and Oversight

From May 19, 2016, to December 31, 2017, this randomized, parallel-group trial was conducted in 32 hospitals in France (24 university-affiliated and 8 non-university-affiliated) belonging to the *Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique* (GRRR-OH). The study protocol was approved by the CPP Ile de France IV St-Louis ethics committee (March 3, 2016, #NIRB00003835/2016/08) and French health authorities (Agence Nationale de Sécurité du Médicament et des Produits de Santé, EudraCT2016-A00220-51). The protocol and statistical analysis plan have been published[14] and are also available in Supplement 1. The trial was overseen by an independent data and safety monitoring board. Written informed consent was obtained from all patients or their proxies.

Patients

Patients were recruited in 32 ICUs having experience and expertise with immunocompromised patients and respiratory care strategies.[8,15] Eligibility criteria were ICU admission; age 18 years or older; AHRF with Pa_{O_2} less than 60 mm Hg or oxygen saturation by pulse oximetry (Sp_{O_2}) less than 90% on room air, or tachypnea greater than 30/min or labored breathing or respiratory distress; need for oxygen flow of 6 L/min or greater; known immunosuppression, defined as use of long-term (>3 months) or high-dose (>0.5 mg/kg/d) steroids, use of other immunosuppressant drugs, solid organ transplantation, solid tumor requiring chemotherapy in the last 5 years, hematologic malignancy regardless of time since diagnosis and received treatments, or primary immune deficiency; and written informed consent from the patient or proxy. Patients with AIDS were not eligible.

Exclusion criteria were imminent death; refusal of study participation by the patient; anatomical factors precluding the use of a nasal cannula; hypercapnia indicating NIV (Pa_{CO_2} ≥50 mm Hg); isolated cardiogenic pulmonary edema indicating NIV; pregnancy or breastfeeding; absence of coverage by the French statutory health care insurance system; and surgery within the last 6 days.

Randomization

Eligible patients were included by investigators in each ICU, then randomly assigned in a 1:1 ratio to either high-flow oxygen therapy or standard oxygen therapy throughout the ICU stay. Randomization was stratified on study center, oxygen flow rate at randomization (>9 L/min vs ≤9 L/min), need for vasopressors, and time since ICU admission (≤2 vs ≥3 days), based on preestablished lists with permutation blocks having a fixed size of 4; block size was concealed. Randomization was achieved using an electronic system incorporated in the electronic case report form to ensure allocation concealment. The nature of the intervention precluded blinding of patients and health care staff. Baseline was defined as time of randomization.

Treatments

All management decisions other than oxygen therapy were made by the managing physicians according to standard practice in each ICU. All patients in both groups received the best standard of care according to local management protocols. The randomly allocated treatment (high-flow oxygen therapy or standard oxygen therapy) was started within 15 minutes after randomization.

In the intervention group, oxygen was delivered only by continuous high-flow oxygen therapy, initiated at 50 L/min and 100% fraction of inspired oxygen (F_{IO_2}), with a subsequent flow rate increase to achieve Sp_{O_2} of 95% or greater, up to at least

50 L/min within the first 3 days then up to 60 L/min as needed. Fraction of inspired oxygen was tapered as possible while maintaining Spo_2 of 95% or greater. In patients who required IMV, high-flow oxygen therapy was used during laryngoscopy and immediately after extubation. Patients with discomfort from high-flow oxygen therapy had their flow rate decreased until the discomfort resolved. Standard oxygen therapy was used in this group only if the nasal cannula generated significant discomfort or skin breakdown, in which case a Venturi mask was used until high-flow oxygen therapy could be tolerated again. Criteria for weaning off high-flow oxygen therapy were improvement in clinical signs of respiratory distress, Pao_2:FIo_2 ratio greater than 300, and ability to maintain Spo_2 of 95% or greater with less than 6 L/min of standard oxygen therapy. After weaning, patients whose oxygen flow was 6 L/min or greater at any time were returned to high-flow oxygen therapy.

In the standard oxygen therapy (control) group, oxygen was delivered via any device or combination of devices used for standard care (nasal prongs or mask with or without a reservoir bag and with or without a Venturi system). Oxygen flow was set to achieve Spo_2 of 95% or greater. High-flow oxygen therapy could be used only for patients with do-not-intubate orders for whom standard oxygen therapy had failed. ICU discharge was considered when patients maintained Spo_2 values of 95% or greater with less than 6 L/min oxygen.

Noninvasive ventilation has been found either nonbeneficial[8] or harmful[10,11,16] and was therefore used only when, and as long as, hypercapnia or pulmonary edema were present.

In both groups, intubation decisions were based on the therapeutic response, clinical status (including Spo_2, respiratory rate, signs of respiratory distress, and bronchial secretion volume). Ventilator settings for IMV complied with the best standard of care.[17]

Study Outcomes

The primary end point was overall mortality within 28 days after randomization.

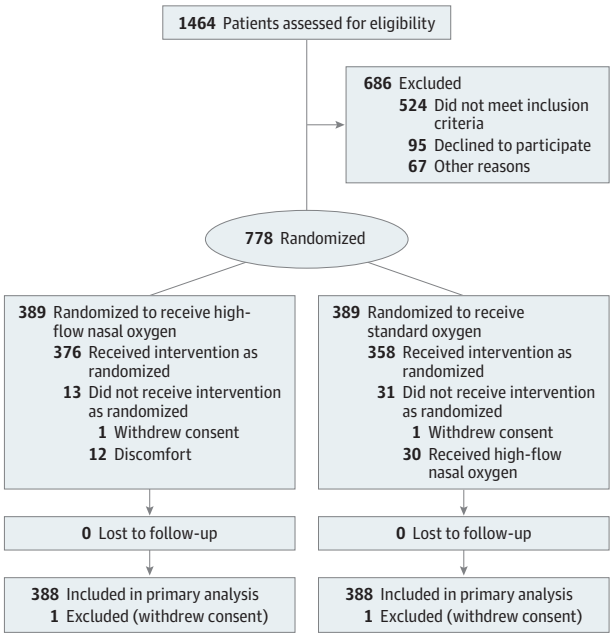
The secondary end points were the proportion of patients requiring IMV by day 28, respiratory rate (normal values, 12-20), lowest Pao_2:FIo_2 ratio (normal values, 500-600; values <300 indicate severe dysfunction of gas exchange in the lungs), patient comfort score (range, 0 [severe discomfort] to 10 [perfect comfort]), dyspnea score (range, 0 [anchor; "no dyspnea"] to 10 ["severe dyspnea"]), ICU and hospital lengths of stay, and incidence of ICU-acquired infections. Minimal clinically important differences were not established.

Data reported in the tables and figures were collected prospectively using an electronic case report form. No blinding of adjudication was performed for outcome assessments.

Statistical Analysis

The protocol first submitted for the grant application was for a noninferiority RCT with a 9% noninferiority margin and with different secondary end points. However, based on the results of the FLORALI trial[10] and as a condition of awarding the grant, the jury requested that the study be changed to a superiority trial. The revised protocol submitted to the institutional review board has been published.[14] Based on an expected 30% day-28 mortality rate in the standard oxygen therapy group with a decrease to 20% in the high-flow oxygen therapy group[11] and with α set at 5%, 779 patients (389 in each group) were required to obtain 90% power for demonstrating an decrease in day-28 mortality.

Figure 1. Flow of Patients Through the HIGH Trial



The number of patients excluded and the reasons for the exclusions were not available in all centers.

A scheduled interim analysis was performed when 100 deaths had occurred, using the Haybittle-Peto boundary, ie, a *P* value threshold of .001 for the interim analysis (because of the risk of inflation of the type I error rate). The interim analysis was reviewed by the independent data and safety monitoring board. To assess the between-group difference in terms of futility or efficacy, the Bayesian posterior probabilities of the day-28 mortality rate and of the log odds ratio were computed, using a uniform noninformative prior; no specific stopping rules were prespecified.

The analysis used the intent-to-treat approach, ie, all patients were analyzed in the group allocated by randomization, with no exclusion after randomization except exclusions for withdrawn consent according to the French regulation at the time. Continuous variables were described as medians (interquartile ranges) and categorical variables as proportions. No participants were excluded from analyses because of missing or incomplete data.

Overall mortality was estimated using the Kaplan-Meier method, with administrative censoring of patients alive in the ICU on day 28. The effect size was evaluated by computing the absolute risk difference with its 95% CI and the hazard ratio (HR) with 95% CI as estimated from univariable Cox regression models; the proportional hazards assumption was checked ($P = .72$), based on weighted residuals.[18] The cumulative incidence of IMV (with death without IMV as a competing risk)

Table 1. Patient Characteristics at Randomization

Characteristic	No. (%) High-Flow Oxygen Therapy (n = 388)	Standard Oxygen Therapy (n = 388)
Demographics		
Age, median (IQR), y	64 (55-70)	63 (56-71)
Sex		
Men	270 (69.6)	247 (63.6)
Women	118 (30.4)	141 (36.4)
Comorbidities		
Chronic		
Respiratory[a]	115 (29.6)	127 (32.7)
Heart failure	23 (5.9)	27 (6.9)
Liver	45 (13.3)	56 (14.4)
Kidney disease	73 (18.8)	69 (20.4)
Charlson Comorbidity Index[b]	5 (4-7)	5 (3-7)
Underlying conditions[c]		
Cancer	294 (75.8)	319 (82.2)
Hematologic malignancies	167 (43.0)	181 (46.6)
Solid tumors	127 (32.7)	138 (35.6)
Immunosuppressive drugs	133 (34.3)	135 (34.8)
Non-transplant-related reasons	89 (22.9)	98 (25.2)
After solid organ transplantation	44 (11.3)	37 (9.5)
Time since diagnosis of underlying condition, median (IQR), mo	6.4 (1-29)	7.0 (0.8-40.0)
Chemotherapy at ICU admission	221/294 (75.2)	228/319 (71.5)
Autologous stem cell transplantation	26/167 (15.6)	22/181 (12.1)
Allogeneic stem cell transplantation	28/167 (16.8)	33/181 (18.2)
Poor performance status (3 or 4)[d]	61 (15.7)	54 (13.9)
Randomization and Other Characteristics		
Randomization		
Day of ICU admission	244 (62.9)	251 (64.7)
Day after ICU admission	77 (19.8)	79 (20.4)
Two days after ICU admission	47 (12.1)	38 (9.8)
≥3 days after	20 (5.1)	20 (5.1)
No. randomized in the postextubation period	14 (4.1)	18 (5.3)
SOFA at randomization, median (IQR)[e]	6 (4-8)	6 (4-8)
SAPSII at randomization, median (IQR)[f]	36 (28-46)	37 (28-48)
Vasopressors at randomization	33 (8.5)	39 (10.0)
Goals of care at randomization		
Full code management	308 (79.4)	309 (79.6)
Do not intubate	13 (3.3)	15 (3.9)
Do not resuscitate	3 (0.7)	1 (0.2)
Time-limited trial of intensive care	35 (9.0)	36 (9.3)
Unknown	29 (7.5)	27 (6.9)
Respiratory status immediately before randomization		
Respiratory rate, median (IQR), /min	33 (28-39)	32 (27-38)
Pao_2:FIO_2 ratio, median (IQR)	136 (96-187)	128 (92-164)
Received standard oxygen therapy before randomization	311 (80.1)	334 (86.1)
Oxygen flow, median (IQR), L/min	10 (6-15)	10 (6-15)
Pao_2 with standard oxygen, median (IQR)	81 (65-111)	75 (65-93)
Estimated Pao_2:FIO_2 ratio (on oxygen), median (IQR)	120 (86-164)	114 (82-149)
Received NIV or high-flow oxygen therapy before randomization		
NIV	25 (6.4)	18 (4.6)
High-flow oxygen therapy	52 (13.4)	36 (9.3)
Pao_2:FIO_2 ratio, median (IQR)	117 (87-173)	108 (76-167)

(continued)

Table 1. Patient Characteristics at Randomization (continued)

Abbreviations: FIO_2, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; NIV, noninvasive ventilation; SOFA, Sequential Organ Failure Assessment; SAPSII, Simplified Acute Physiology Score version II.

[a] Chronic respiratory insufficiency includes obstructive and restrictive chronic respiratory disease.

[b] Contains 19 categories of comorbidities and predicts the 10-year mortality for a patient who may have a range of comorbid conditions. The physician assigns each condition a score of 1, 2, 3, or 6, depending on the patient's risk of dying associated with the condition; higher scores indicate greater comorbidity, resulting in an index ranging from 19 (low risk of death) to 114 (high risk of death). It is measured by physicians.

[c] Main hematologic malignancies were acute myeloid leukemia (n = 123), non-Hodgkin lymphoma (n = 97), and myeloma (n = 41). Solid tumors primarily affected the lung (n = 72), digestive tract (n = 60), and breast (n = 30). Immunosuppressive drugs included steroids in 174 patients; the main transplanted solid organs were the kidney (n = 46) and liver (n = 19).

[d] Indicates patients who are bedridden or dependent.

[e] SOFA score collects information on the presence and intensity of respiratory, coagulation, hemodynamic, neurologic, liver, and kidney failures. Each organ is assessed from 0 (no failure) to 4 (worst possible failure); score range, 0 (no organ failure) to 24 (all organ failures). The highest value was recorded. A score between 7 and 9 indicates a mortality risk of 15% to 20%.

[f] SAPSII score was calculated as previously reported.[20] The score ranges from 0 (predicted hospital mortality of 0%) to 163 (predicted hospital mortality of 100%). A score of 36 indicates a mortality risk of 18% to 20%.

in each group was estimated using a nonparametric estimator and compared using the Gray test[19]; effect size was measured using a univariable cause-specific Cox model. The proportions of ICU-acquired infections in the 2 groups were compared by χ^2 test. The Wilcoxon rank-sum test was chosen for comparisons of the visual analog scale scores for comfort and dyspnea, respiratory rate, and ICU length of stay. Relative risk was estimated as a measure of treatment effect in terms of ICU and hospital mortality.

Effect of high-flow oxygen therapy vs standard oxygen therapy was measured using HRs estimated from Cox regression models in subgroups defined by stratification variables, then displayed in forest plots. The Gail and Simon interaction test was then applied to assess whether these estimates were homogeneous across subsets ie, to test for quantitative interactions between the study treatment and stratification variables (baseline oxygen flow rate, need for vasopressors, and time from ICU admission to randomization).

Because there was no handling of the potential for type I error inflation due to multiple comparisons of secondary analyses, those analyses should be considered exploratory. Post hoc analyses included the search for site effect in terms of the primary end point, using frailty model and subset analyses in intubated patients.

Table 2. Primary and Secondary End Points[a]

End Points	No. (%) High-Flow Oxygen Therapy (n = 388)	No. (%) Standard Oxygen Therapy (n = 388)	Mean Difference, % (95% CI)[b]	Relative Difference (95% CI)	*P* Value
Primary					
All-cause day-28 mortality	138 (35.6)	140 (36.1)	−0.5 (−7.3 to 6.3)	HR, 0.98 (0.77 to 1.24)	.94
Secondary					
Invasive mechanical ventilation[c]	150 (38.7)	170 (43.8)	−5.1 (−12.3 to 2.0)	HR, 0.85 (0.68 to 1.06)[d]	.17
ICU-acquired infection	39 (10.0)	41 (10.6)	−0.6 (−4.6 to 4.1)	HR, 1.01 (0.96 to 1.06)[d]	.91
ICU mortality	123 (31.7)	122 (31.4)	0.3 (−6.3 to 6.8)	RR, 1.01 (0.82 to 1.24)	.64
Hospital mortality	160 (41.2)	162 (41.7)	−0.5 (−7.5 to 6.4)	RR, 0.99 (0.84 to 1.17)	.77
Length of stay, median (IQR), d					
ICU	8 (4-14)	6 (4-13)	0.6 (−1.0 to 2.2)	NA[e]	.07
Hospital	24 (14-40)	27 (15-42)	−2 (−7.3 to 3.3)	NA[e]	.60

Abbreviations: HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; NA, not available; RR, relative risk.

[a] No patients were lost to follow-up.

[b] Mean difference was defined across intervention and controls groups by absolute risk difference for binary outcomes (mortality, invasive mechanical ventilation, infections) and difference in means for quantitative outcomes (lengths of stay in ICU and in hospital).

[c] The use of invasive mechanical ventilation was based on the clinical response to oxygen or noninvasive ventilation, clinical status (including oxygen saturation by pulse oximetry [Spo_2], respiratory rate, signs of respiratory distress, and bronchial secretion volume), and patient adherence to noninvasive ventilation. Criteria for invasive mechanical ventilation were severe hemodynamic instability (requiring norepinephrine or epinephrine >0.3 µg/kg/min) or cardiorespiratory arrest or ongoing myocardial infarction, severe encephalopathy (Glasgow Coma Scale score <11), severe airway secretion retention or worsening of respiratory distress (SpO_2 <92% or respiratory rate >40/min regardless of oxygen flow rate or use of accessory respiratory muscles), inability to maintain Pao_2 greater than 65 mm Hg with fraction of inspired oxygen (Fio_2) greater than 0.6 or dependency on noninvasive ventilation with inability to remain off noninvasive ventilation for longer than 2 hours, greater than 50% increase in the time on noninvasive ventilation from one day to the next (eg, 6 hours of noninvasive ventilation on day 1, then >9 hours on day 2).

[d] Cause-specific HR.

[e] Effect of high-flow oxygen therapy on length-of-stay measures could not be expressed by HRs.

All reported *P* values are 2-sided; $P < .05$ was considered statistically significant. All analyses were performed using R version 3.1.0 (R Foundation for Statistical Computing [http://www.R-project.org/]).

Results

Patients

Of 778 patients (median age, 64 [interquartile range {IQR}, 54-71] years; 259 [33.3%] women)randomized to high-flow nasal oxygen therapy (n = 389) and standard oxygen therapy (n= 389), 776 (99.7%; n = 388 in each group) completed the trial (**Figure 1**). No patient was lost to follow-up. Baseline characteristics were evenly distributed between the 2 groups (**Table 1**). Malignancies and their treatments were the main causes of immunosuppression.

At randomization, median respiratory rate was 33 (IQR, 28-39) and 32 (IQR, 27-38) and median Pao_2:Fio_2 ratio was 136 (IQR, 96-187) and 128 (IQR, 92-164) in the high-flow oxygen therapy and standard oxygen therapy groups, respectively. The median Sequential Organ Failure Assessment score was 6 (IQR, 4-8) in both groups (Table 1). The leading cause of AHRF was bacterial pneumonia (n = 320), followed by invasive fungal infection (n = 91, including 59 cases of *Pneumocystis* pneumonia) and lung involvement from the underlying disease (n = 80). At randomization, 32 patients (4.1%) had do not intubate/do not resuscitate orders in place (16 in each group) (Table 1). In addition, 37 patients (4.8%) who did not have do not intubate/do not resuscitate orders in place at randomization acquired this status during the ICU stay (20 in the high-flow oxygen therapy group, 17 in the standard oxygen therapy group).

Interventions

All patients in the intervention group received continuous high-flow oxygen therapy starting immediately after randomization, with an oxygen flow of 50 L/min or greater and Fio_2 of 100%. Intolerance required switching from high-flow oxygen therapy to a Venturi mask in 12 patients (3%), of whom 3 died. In the standard oxygen therapy group, median oxygen flow was 10 (IQR, 6-15) L/min through a thin nasal cannula (29.5%), mask with no bag (23.5%), mask with a bag (40.6%), or Venturi mask (6.4%). Of the 30 patients (7.7%) in the standard oxygen therapy group with do-not-intubate orders who were switched to high-flow oxygen therapy after failure of standard oxygen therapy, 14 (46.7%) died.

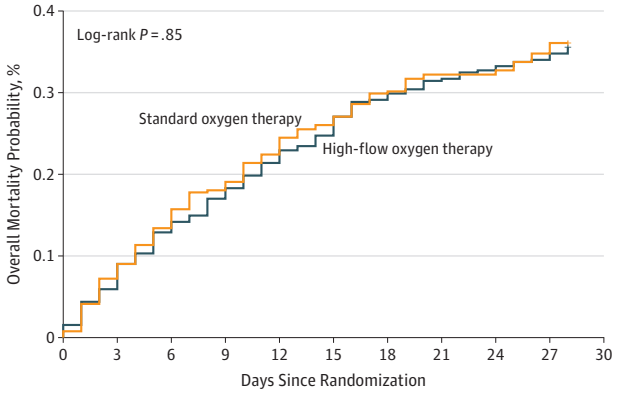
Interim Analysis

Interim analysis, performed as planned after 100 deaths, yielded a *P* value of .94; the trial was therefore continued.

Primary Outcome

By day 28 after randomization, 138 of 388 patients (35.6%) randomized to high-flow oxygen therapy and 140 of 388 patients (36.1%) randomized to standard oxygen therapy had died, and day-28 mortality was not significantly different between groups (risk difference, −0.5% [95% CI, −7.3% to +6.3%]; HR, 0.98 [95% CI, 0.77-1.24]; $P = .94$) (**Table 2** and **Figure 2**). There was no significant interaction between the intervention effect and the 3 predefined subgroups (**Figure 3**).

Figure 2. Probability of Day-28 Mortality in Immunocompromised Patients With Acute Respiratory Failure Receiving High-Flow Oxygen Therapy or Standard Oxygen Therapy



No. at risk

High-flow oxygen therapy	388	365	338	322	305	292	275	266	261	256	0
Standard oxygen therapy	388	360	336	318	301	287	272	263	263	253	0

Median survival was not reached in either group.

Secondary Outcomes

Need for IMV was not significantly different between groups, required in 150 patients (38.7%) receiving high-flow oxygen therapy and 170 patients (43.8%) receiving standard oxygen therapy (absolute risk difference, −5.1% [95% CI, −12.3% to +2.0%]; cause-specific HR, 0.85 [95% CI, 0.68 to 1.06]; P = .17). The cumulative incidence of intubation was not significantly different between groups (eFigure 1 in Supplement 2). With high-flow oxygen therapy vs standard oxygen therapy, the respiratory rate was significantly lower after 6 hours (25/min vs 26/min; mean difference, −1.8 [95% CI, −3.2 to −0.3]), and Pao_2:FIO_2 ratio was significantly higher until day 4 (150 vs 119; mean difference, 19.5 [95% CI, 4.4 to 34.6]) (eFigure 2 and eTable in Supplement 2). Comfort and dyspnea scores were not significantly different between groups at any time (eFigure 3 in Supplement 2). There was no significant difference in ICU-acquired infections (10.0% vs 10.6%; absolute risk difference, −0.6% [95% CI, −4.6% to +4.1%]), ICU length of stay (8 vs 6 days; mean difference, 0.6 days[95% CI, −1.0 to +2.2]), or hospital length of stay (24 vs 27 days; mean difference, −2 days [95% CI, −7.3 to +3.3]). None of the other secondary outcomes differed significantly between groups (Table 2).

Post Hoc Outcomes

There was no significant center effect on mortality (P = .33) or intubation rate (P = .07). In the overall population, vasopressors and renal replacement therapy were needed in 153 patients (19.7%) randomized to high-flow oxygen therapy and 31 patients (4%) randomized to standard oxygen therapy, with no statistical difference between groups.

Duration of high-flow oxygen therapy was 2 (IQR, 1-5) days, and all patients were discharged from the ICU with standard oxygen therapy (3 L/min, with no significant difference between groups). In patients who needed IMV, median time from randomization to intubation was 1 (IQR, 0-2) day, and this did not differ significantly between groups (mean difference, −0.5 days [95% CI, −1.2 to 0.1]). Mortality in intubated patients was not significantly different (55.3% with high-flow oxygen therapy vs 52.3% with standard oxygen therapy; absolute risk difference, +3% [95% CI, −8.5% to +14.5%]) (P = .65). Decisions to limit treatment were made for 170 patients (21.9%), of whom 135 (79.4%) died before day 28, with no significant difference between groups. Day-28 mortality was not significantly different in patients with and without cancer as the cause of immunosuppression (absolute risk difference, +1.8% [95% CI, −10.8% to +14.3%]) (P = .50).

Day-90 mortality did not differ significantly between groups (46.9% with high-flow oxygen therapy, 48.2% with standard oxygen therapy).

Discussion

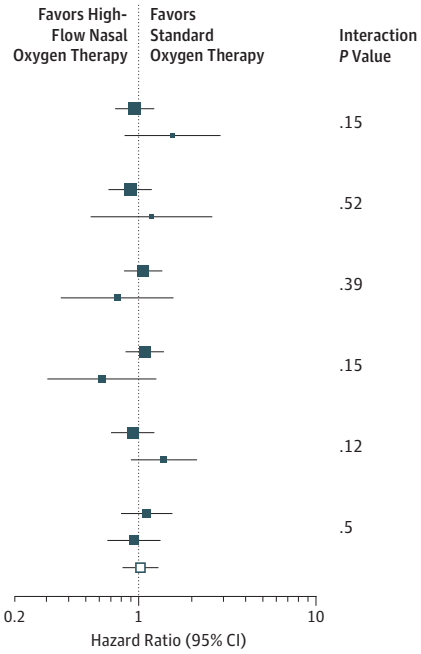
This RCT found no significant survival benefits with high-flow oxygen therapy compared with standard oxygen therapy in immunocompromised patients with AHRF. Neither were significant differences found for intubation requirements, ICU-acquired infections, subjective dyspnea and comfort, or ICU length of stay. These results suggest that attention to oxygenation strategies may not be the best means of improving survival among immunocompromised patients with AHRF.

Improving oxygenation is relevant in all patients with AHRF, but even more so in those who are immunocompromised. These patients are more severely hypoxemic[11] and most often require a diagnostic strategy[5,21,22] for which high-flow oxygen therapy, which effectively improves oxygenation, can translate into improved outcomes. However, this trial did not find a significantly reduced intubation rate in immunocompromised patients receiving high-flow oxygen therapy. These results agree with those of 2 post hoc analyses showing no significant clinical benefits from high-flow oxygen therapy compared with standard oxygen therapy in immunocompromised patients with AHRF.[11,12] Noninvasive ventilation was either neutral[8] or harmful[11] in that population. Also, both standard oxygen therapy and high-flow oxygen therapy are valid options in immunocompromised patients with AHRF.

Figure 3. Hazard Ratios for Day-28 Mortality (Primary Outcome) and Cumulative Incidence of Mechanical Ventilation, Overall and in Predefined Subgroups, in Immunocompromised Patients With Acute Respiratory Failure Receiving High-Flow Oxygen Therapy or Standard Oxygen Therapy

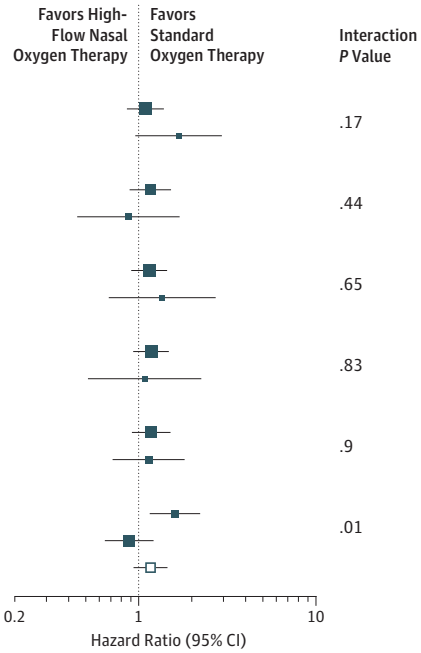
A Day-28 mortality

Subset	Deaths at Day 28/Total No. of Patients: High-Flow Nasal Oxygen Therapy	Deaths at Day 28/Total No. of Patients: Standard Oxygen Therapy	Hazard Ratio (95% CI)	Interaction *P* Value
ICU admission to randomization, d				
0-1	120/321	118/330	0.95 (0.74-1.22)	.15
≥2	18/67	22/58	1.55 (0.83-2.90)	
Pao_2: FIO_2 ratio				
<200	99/237	95/251	0.89 (0.68-1.19)	.52
≥200	16/65	10/35	1.18 (0.54-2.60)	
Oxygen flow at randomization, L/min				
≤9	122/348	127/347	1.06 (0.83-1.36)	.39
>9	16/40	13/41	0.76 (0.36-1.57)	
Catecholamines				
No	121/355	126/349	1.08 (0.84-1.39)	.15
Yes	17/33	14/39	0.62 (0.31-1.26)	
Unknown diagnosis				
No	99/297	95/303	0.93 (0.70-1.23)	.12
Yes	39/91	45/85	1.39 (0.90-2.13)	
Hematologic malignancy				
No	66/199	72/198	1.11 (0.79-1.55)	.5
Yes	64/167	65/181	0.94 (0.67-1.33)	
All patients	138/388	140/388	1.02 (0.81-1.29)	



B Cumulative incidence of IMV

Subset	No. With IMV at Day 28/Total No. of Patients: High-Flow Nasal Oxygen Therapy	No. With IMV at Day 28/Total No. of Patients: Standard Oxygen Therapy	Hazard Ratio (95% CI)	Interaction *P* Value
ICU admission to randomization, d				
0-1	128/321	142/330	1.1 (0.87-1.40)	.17
≥2	22/67	28/58	1.69 (0.96-2.95)	
Pao_2: FIO_2 ratio				
<200	99/237	117/251	1.17 (0.90-1.53)	.44
≥200	27/65	13/35	0.88 (0.46-1.71)	
Oxygen flow at randomization, L/min				
≤9	136/348	151/347	1.15 (0.91-1.45)	.65
>9	14/40	19/41	1.37 (0.68-2.72)	
Catecholamines				
No	137/355	154/349	1.18 (0.94-1.49)	.83
Yes	13/33	16/39	1.09 (0.52-2.26)	
Unknown diagnosis				
No	114/297	135/303	1.18 (0.92-1.52)	.9
Yes	36/91	35/85	1.15 (0.72-1.82)	
Hematologic malignancy				
No	61/199	89/198	1.61 (1.16-2.23)	.01
Yes	78/167	77/181	0.89 (0.65-1.22)	
All patients	150/388	170/388	1.17 (0.94-1.46)	



Square sides of data markers are proportional to subgroup sizes, with the exception of the open squares in "All patients" rows. Error bars indicate 95% confidence intervals. The Gail and Simon test for interaction was used.

Strengths of this trial should be noted. First, to the best of our knowledge, it is the largest trial to date enrolling immunocompromised patients with AHRF. Second, the assumptions made for the sample size estimation were met. Third, the participation of a large number of ICUs in university-affiliated and community hospitals supports external validity. Fourth, the results are consistent with a pilot trial and 2 post hoc studies in smaller numbers of patients.[11-13]

In the current trial, high-flow oxygen therapy compared with standard oxygen therapy failed to decrease the intubation rate, despite producing better oxygenation. Moreover, in agreement with results from a pilot trial in immunocompromised patients, comfort and dyspnea were not improved.[13] RCTs in unselected patients with AHRF have produced conflicting results when high-flow oxygen therapy was used for AHRF,[23] during intubation,[24-26] after extubation,[27-29] or after thoracic surgery.[30,31] These apparent contradictions, combined with the lower mortality with high-flow oxygen therapy in 1 trial,[10] led to the choice of mortality as the primary end point.

This study has several limitations. First, all participating centers were located in France, raising questions about the general applicability of these findings. Second, the NIV-high-flow oxygen therapy combination was not assessed. However, NIV failed to provide clinical benefits in immunocompromised patients in an RCT,[8] and the NIV-high-flow oxygen therapy combination was associated with increased mortality in another RCT.[10,11] Third, the lack of blinding may have affected the likelihood of differential treatment or assessments of outcomes. Fourth, a minimal Spo_2 of 95% was targeted without having an upper target. However, findings have strongly suggested that a conservative protocol for oxygen therapy vs conventional therapy resulted in lower mortality rates.[32,33] Fifth, estimates of treatment effect were not adjusted on stratification factors, and this may have resulted in an overestimation of the *P* value for the difference between end point rates in treatment groups. Sixth, potential risk of false-positive findings attributable to repeated testing should be taken into account and results of the secondary analyses considered as exploratory.

Conclusions

Among critically ill immunocompromised patients with acute respiratory failure, high-flow oxygen therapy did not significantly decrease day-28 mortality compared with standard oxygen therapy.

ARTICLE INFORMATION

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Author Contributions: Dr Azoulay had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Chevret conducted and is responsible for the data analysis.
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Acquisition, analysis, or interpretation of data: All authors.
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Critical revision of the manuscript for important intellectual content: Azoulay, Lemiale, Mokart, Nseir, Argaud, Pène, Bruneel, Klouche, Barbier, Reignier, Berrahil-Meksen, Louis, Constantin, Mayaux, Wallet, Kouatchet, Peigne, Perez, Girault, Jaber, Oziel, Nyunga, Terzi, Bouadma, Lebert, Lautrette, Bigé, Raphalen, Papazian, Darmon, Chevret, Demoule.
Statistical analysis: Lemiale, Chevret.
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Administrative, technical, or material support: Azoulay, Mokart, Klouche, Berrahil-Meksen, Théodose, Oziel, Nyunga, Terzi, Chevret, Demoule.
Supervision: Azoulay, Mokart, Klouche.

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Additional Contributions: Antoine Rabbat, MD (Hopital Cochin, Paris, France), contributed to the study by providing a high level of medical expertise

in the care if immunocompromised patients. He helped design the trial, defend the application, and included patients but died before publication.

Data Sharing Statement: See Supplement 3.

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