EDITORIAL

The Changing Landscape of Noninvasive Ventilation in the Intensive Care Unit

Bhakti K. Patel, MD; John P. Kress, MD

Traditionally, endotracheal intubation has been used as a treatment for patients with respiratory failure who require mechanical ventilation. Although intubation can be lifesaving, it is also associated with significant morbidity.[1] Immunocompromised patients with acute hypoxemic respiratory failure are at particularly high risk; these patients often require high levels of ventilatory support (ie, positive end-expiratory pressure [PEEP] and fractions of inspired oxygen [F_{IO_2}]). Intubated patients usually require sedative medications, analgesic agents, or both and are at risk for many complications seen in the intensive care unit (ICU), such as ventilator-associated pneumonia, ICU-acquired weakness,[2] venous thromboembolism,[3] delirium, and cognitive dysfunction.[4] As such, these patients typically have a high associated mortality, estimated at approximately 50%.[5]

Related article

Therefore, in modern ICU care, noninvasive ventilation is used frequently for the care of patients with acute respiratory failure. Specifically, this intervention can improve gas exchange and reduce the work of breathing without requiring an artificial airway. Consequently, patients treated with noninvasive ventilation may avoid some of the adverse consequences of invasive mechanical ventilation. The most compelling evidence for the benefits of noninvasive ventilation is from studies involving patients with exacerbations of chronic obstructive pulmonary disease[6] and acute cardiogenic pulmonary edema.[7] The benefits of noninvasive ventilation in hypoxemic immunocompromised patients are less compelling. Two small, randomized clinical trials demonstrated that use of noninvasive ventilation was associated with a substantial decrease in rates of endotracheal intubation, ICU complications, and mortality.[5,8] However, these studies are old, and other studies that involved a heterogeneous population of patients with acute hypoxemic respiratory failure demonstrated high rates of treatment failure with noninvasive ventilation.[9,10]

Over the last 2 decades, the technology of noninvasive ventilation has changed substantially. The ventilators used in the 1990s delivered pressure through the ventilator circuit with room air as the source of fresh gas flow,[6] with flow rates that were relatively low (ie, 10 to 35 L/min). These flow rates could be supplemented by oxygen delivered via a side port tubing connection. However, given that room air was the source of most of the fresh gas flow through the ventilator, the highest F_{IO_2} that could be delivered was typically limited to 30% to 40%. Such ventilators were of limited utility in the care of patients requiring higher F_{IO_2} levels. In addition, the ventilator interface was a rubber face mask that was often prone to air leakage when high pressures were needed.[6] In contrast, modern noninvasive ventilation involves use of a ventilator with the fresh gas flow source coming directly from the medical oxygen and medical air sources. These connections allow for high pressure and flow and an F_{IO_2} that can be titrated from 21% to 100% as needed. Furthermore, the interfaces now available for noninvasive ventilation administration include more compliant masks of various sizes; these tend to be much more comfortable, particularly for patients with acute hypoxemic respiratory failure, who often require higher levels of PEEP, higher driving pressures, or both.

Not only has noninvasive ventilation changed, but the case mix and care of critically ill patients with immunocompromise has also changed considerably over the last 20 years. Together, these issues have fueled controversy over the role of noninvasive ventilation for acute hypoxemic respiratory failure in this patient population. Therefore, Lemiale and colleagues[11] tested the efficacy of noninvasive ventilation in immunocompromised patients in a multicenter randomized clinical trial, the results of which are published in this issue of *JAMA*. This study has many strengths. The investigators are an experienced group with a high level of expertise in the use of noninvasive ventilation for respiratory failure. The study was carefully designed, with excellent adherence to the protocol and 100% long-term follow-up. Even though it was impossible to blind the study groups, the end points of 28-day mortality and need for endotracheal intubation are objective and are subject to very low risk for bias affecting the outcome.

In contrast to studies from more than a decade prior, the investigators in the current trial were unable to demonstrate a mortality benefit, with 24.1% mortality in the group with early use of noninvasive ventilation (46 deaths among 191 patients) vs 27.3% mortality in the group receiving oxygen alone (50 deaths among 183 patients) (P = .47). Furthermore, intubation rates were not different between the groups (38.2% in the noninvasive ventilation group vs 44.8% in the oxygen alone group, P = .20).

However, before the use of noninvasive ventilation in immunocompromised patients is abandoned, these findings should be contextualized by advances in ICU care in the past 15 years, since publication of the seminal articles on this intervention in this type of patient population.[5,8]

First, overall mortality in the immunocompromised critically ill population has declined with advances in targeted

chemotherapy, prophylactic use of antibiotics, and improved supportive care.[12] In their study, Lemiale et al anticipated a higher baseline mortality of 35%, which limited their power to detect a mortality difference. Second, the patients enrolled in the earlier trials by Hilbert et al[8] and Antonelli et al[5] had greater degrees of tachypnea compared with patients in the current study (upper respiratory rate, 35-38/min vs 25/min), suggesting a greater severity of respiratory failure in the previous trials. However, unlike the earlier studies of noninvasive ventilation in acute hypoxemic respiratory failure,[5,8] Lemiale et al did not report a severity of illness score (eg, Simplified Acute Physiology Score).[13] Given the much higher respiratory rates and higher mortality in the earlier trials, it may be that the patients in this current trial had lower acuity of illness. Third, in the study by Lemiale et al, a greater proportion of patients in the oxygen alone group than in the noninvasive ventilation group received high-flow oxygen via nasal cannula. Given the recent findings of improved mortality with high-flow nasal cannula compared with noninvasive ventilation,[14] perhaps the benefits from noninvasive ventilation were diluted with the use of this therapy. As the authors suggest, a comparison of high-flow oxygen and noninvasive ventilation for the management of acute hypoxemic respiratory failure in immunocompromised patients warrants further study. Therefore, all of these factors may have contributed to regression to the mean for the clinical outcomes in this negative trial.

The physiologic goals of noninvasive ventilation in the treatment of acute hypoxemic respiratory failure are to recruit lung with the proper use of PEEP and unload the respiratory muscles with the addition of pressure support ventilation. Physiologic studies examining use of noninvasive ventilation in acute lung injury have suggested that a PEEP of at least 10 cm H_2O is required to significantly improve Pao_2:FIO_2 ratio with therapy.[15] Furthermore, titration of PEEP and pressure support ventilation titration can be limited by the face mask leak and poor patient tolerance, even with modern ventilators and face mask interfaces, thus decreasing the efficacy of noninvasive ventilation delivered via face mask. With additional efforts to continue to reduce the percentage of critically ill patients who require invasive mechanical ventilation, alternative strategies for noninvasive ventilation that minimize face mask leak, improve oxygenation, and decrease work of breathing with alternative interfaces such as high-flow nasal cannula will need further investigation.

ARTICLE INFORMATION

Author Affiliations: Section of Pulmonary and Critical Care, Department of Medicine, University of Chicago, Chicago, Illinois.

Corresponding Author: John P. Kress, MD, Section of Pulmonary and Critical Care, Department of Medicine, University of Chicago, 5841 S Maryland, MC 6026, Chicago, IL 60637 (jkress@medicine.bsd.uchicago.edu).

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Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Noninvasive Ventilation vs Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure
A Randomized Clinical Trial

Virginie Lemiale, MD; Djamel Mokart, MD; Matthieu Resche-Rigon, MD, PhD; Frédéric Pène, MD, PhD; Julien Mayaux, MD; Etienne Faucher, MD; Martine Nyunga, MD; Christophe Girault, MD, PhD; Pierre Perez, MD; Christophe Guitton, MD, PhD; Kenneth Ekpe, MD; Achille Kouatchet, MD; Igor Théodose, MS; Dominique Benoit, MD, PhD; Emmanuel Canet, MD; François Barbier, MD, PhD; Antoine Rabbat, MD; Fabrice Bruneel, MD; Francois Vincent, MD; Kada Klouche, MD, PhD; Kontar Loay, MD; Eric Mariotte, MD; Lila Bouadma, MD, PhD; Anne-Sophie Moreau, MD; Amélie Seguin, MD; Anne-Pascale Meert, MD, PhD; Jean Reignier, MD, PhD; Laurent Papazian, MD, PhD; Ilham Mehzari, MD; Yves Cohen, MD, PhD; Maleka Schenck, MD; Rebecca Hamidfar, MD; Michael Darmon, MD, PhD; Alexandre Demoule, MD, PhD; Sylvie Chevret, MD, PhD; Elie Azoulay, MD, PhD; for the Groupe de Recherche en Réanimation Respiratoire du patient d'Onco-Hématologie (GRRR-OH)

IMPORTANCE Noninvasive ventilation has been recommended to decrease mortality among immunocompromised patients with hypoxemic acute respiratory failure. However, its effectiveness for this indication remains unclear.

OBJECTIVE To determine whether early noninvasive ventilation improved survival in immunocompromised patients with nonhypercapnic acute hypoxemic respiratory failure.

DESIGN, SETTING, AND PARTICIPANTS Multicenter randomized trial conducted among 374 critically ill immunocompromised patients, of whom 317 (84.7%) were receiving treatment for hematologic malignancies or solid tumors, at 28 intensive care units (ICUs) in France and Belgium between August 12, 2013, and January 2, 2015.

INTERVENTIONS Patients were randomly assigned to early noninvasive ventilation (n = 191) or oxygen therapy alone (n = 183).

MAIN OUTCOMES AND MEASURES The primary outcome was day-28 mortality. Secondary outcomes were intubation, Sequential Organ Failure Assessment score on day 3, ICU-acquired infections, duration of mechanical ventilation, and ICU length of stay.

RESULTS At randomization, median oxygen flow was 9 L/min (interquartile range, 5-15) in the noninvasive ventilation group and 9 L/min (interquartile range, 6-15) in the oxygen group. All patients in the noninvasive ventilation group received the first noninvasive ventilation session immediately after randomization. On day 28 after randomization, 46 deaths (24.1%) had occurred in the noninvasive ventilation group vs 50 (27.3%) in the oxygen group (absolute difference, −3.2 [95% CI, −12.1 to 5.6]; $P = .47$). Oxygenation failure occurred in 155 patients overall (41.4%), 73 (38.2%) in the noninvasive ventilation group and 82 (44.8%) in the oxygen group (absolute difference, −6.6 [95% CI, −16.6 to 3.4]; $P = .20$). There were no significant differences in ICU-acquired infections, duration of mechanical ventilation, or lengths of ICU or hospital stays.

CONCLUSIONS AND RELEVANCE Among immunocompromised patients admitted to the ICU with hypoxemic acute respiratory failure, early noninvasive ventilation compared with oxygen therapy alone did not reduce 28-day mortality. However, study power was limited.

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Editorial

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Groupe de Recherche en Réanimation Respiratoire du patient d'Onco-Hématologie (GRRR-OH) members are listed at the end of this article.

Corresponding Author: Elie Azoulay, MD, PhD, Medical Intensive Care Unit, Hôpital Saint-Louis, 1 Avenue Claude Vellefaux, 75010 Paris, France (elie.azoulay@sls.aphp.fr).

Section Editor: Derek C. Angus, MD, MPH, Associate Editor, *JAMA* (angusdc@upmc.edu).

The number of patients living with immune deficiencies is increasing steadily.[1,2] These patients are at high risk for life-threatening complications, especially acute respiratory failure warranting admission to the intensive care unit (ICU).[3] Mortality in this situation has ranged from 40% to 90% and remains high, despite improvements in recent years.[4,5] Invasive mechanical ventilation strongly predicts mortality,[6] possibly because of the risks of ventilation itself, which has prompted efforts to determine whether acute respiratory failure can be safely managed without intubation.

In a single-center randomized trial of 52 patients admitted to the ICU with early-stage hypoxemic acute respiratory failure, noninvasive ventilation significantly decreased the need for intubation and increased survival to hospital discharge when compared with administration of oxygen through a Venturi mask.[7] Subsequently, use of noninvasive ventilation as a first-line strategy for immunocompromised patients presenting in acute respiratory failure was incorporated into international guidelines.[8] However, this recommendation remains debated,[9] as it was informed primarily by a single small randomized trial in which the control group had a high mortality rate. Moreover, the trial[7] was conducted in 1998-1999, and, since then, outcomes of critically ill immunocompromised patients have improved considerably.[4-6,10,11] Furthermore, failure of noninvasive ventilation followed by delayed intubation may increase mortality.[12]

We therefore designed the multicenter iVNIctus randomized controlled trial to test the hypothesis that early noninvasive ventilation, compared with oxygen only, decreased all-cause day-28 mortality in immunocompromised patients admitted to the ICU with hypoxemic acute respiratory failure.

Methods

Study Design and Oversight

From August 2013 to January 2015, we conducted this randomized, parallel-group trial in 28 hospitals in France and Belgium (21 university and 7 non-university-affiliated hospitals belonging to the Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique (GRRR-OH) (Study protocol available in Supplement 1). The study protocol was approved by the French ethics committee CPP Ile de France IV, Saint-Louis, the French health authorities, and the ethics committees of the 2 Belgian hospitals. The protocol and statistical analysis plan were published.[13] Informed consent was obtained from all patients. The trial was overseen by an independent data and safety monitoring board. The 2 funding sources (Legs Poix and OUTCOMEREA) are academic nonprofit organizations with no role in the study.

Patients

Patients were recruited in 28 ICUs where the staff had considerable experience and expertise with immunocompromised patients and noninvasive ventilation and where admission policies for such patients were similar.[13] Eligibility criteria were 18 years or older; acute hypoxemic respiratory failure (PaO_2 <60 mm Hg on room air, or tachypnea >30/min, or labored breathing or respiratory distress or dyspnea at rest); respiratory symptom duration less than 72 hours; and immune deficiency defined as hematologic malignancy or solid tumor (active or in remission for less than 5 years), solid organ transplant, long-term (>30 days) or high-dose (>1 mg/kg/d) steroids, or any immunosuppressive drug taken in a high dosage or for more than 30 days. Patients meeting these criteria were assessed for contraindications to noninvasive ventilation (pneumothorax, vomiting, inability to protect the airway, or copious respiratory secretions). Other exclusion criteria were hypercapnia defined as partial pressure of arterial carbon dioxide greater than 50 mm Hg, need for immediate invasive mechanical ventilation, cardiogenic acute pulmonary edema, need for epinephrine or norepinephrine greater than 0.3 µg/kg/min, ongoing myocardial infarction or acute coronary syndrome, impaired consciousness (Glasgow Coma Scale score <13), do-not-intubate decision, long-term oxygen therapy, postoperative acute respiratory failure, refusal of the patient or family to participate in the study, pregnancy or breastfeeding, and absence of national statutory health insurance coverage.

Randomization

Enrolled patients were randomly assigned in a 1:1 ratio to receive either noninvasive ventilation or oxygen throughout the ICU stay. Randomization was stratified by study center, oxygen flow rate at randomization (> or ≤9 L/min), and cause of immunosuppression (malignancy vs other), based on preestablished lists constructed via permutation blocks of concealed variable size. A centralized Internet-based randomization procedure was used. The nature of the intervention precluded blinding of the patients and clinicians. Baseline was defined as the time of randomization. Investigators were aware that the trial was studying early noninvasive ventilation, rather than noninvasive ventilation among patients who would otherwise have been promptly intubated.

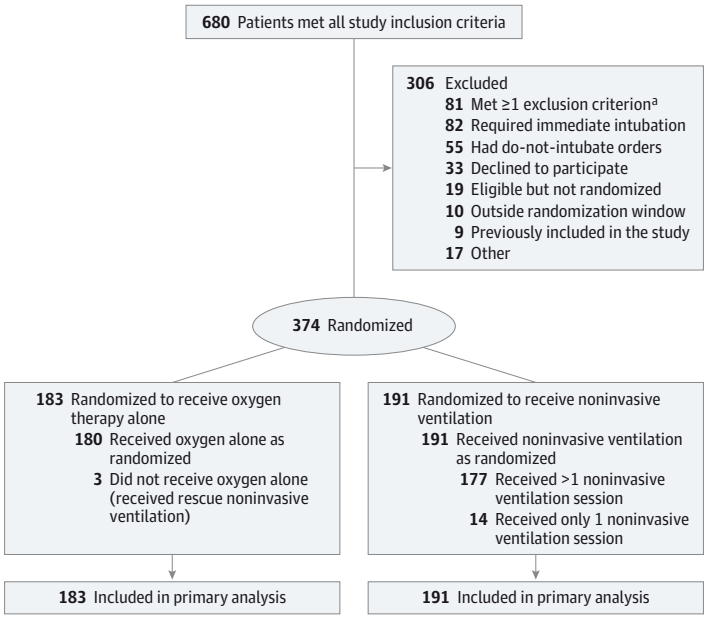
Study Treatments

All management decisions other than the use of noninvasive ventilation or oxygen were made by the managing physicians according to standard practice in each ICU. Diagnostic tests to identify the cause of respiratory failure were chosen based on previous studies by the GRRR-OH.[6,10,14]

In both groups, oxygenation modalities and the use of high-flow nasal oxygen were at the clinician's discretion. Noninvasive ventilation was not allowed for patients allocated to the oxygen group except, if needed, for preoxygenation before intubation or for up 2 hours to improve the safety of bronchoscopy and bronchoalveolar lavage.

In the noninvasive ventilation group, the intervention was started immediately after randomization. A face mask connected to an ICU ventilator was used, with pressure support applied in noninvasive ventilation mode. The pressure-support level was adjusted to obtain an expired tidal volume of 7 to 10 mL/kg of ideal body weight, with an initial positive

Figure 1. Flow of Participants Through Study



[a] The reasons for the exclusion were not available in all centers.

end-expiratory pressure between 2 and 10 cm H_2O. The fraction of inspired oxygen and positive end-expiratory pressure levels were adjusted to maintain the peripheral capillary oxygen saturation (Spo_2) at 92% or greater. The recommended duration of noninvasive ventilation was a 60-minute session every 4 hours, for at least 2 days. Expiratory tidal volumes, respiratory and heart rates, Spo_2, and consciousness were monitored.

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), and patient's adherence to noninvasive ventilation. Ventilator settings for invasive mechanical ventilation complied with the best standard of care.[15-18] Noninvasive ventilation was resumed after resolution of the signs of respiratory distress and was stopped when signs of respiratory failure had disappeared between 2 sessions of noninvasive ventilation.

Study Outcomes

The primary study outcome was all-cause mortality within 28 days after randomization. Secondary outcomes were exploratory and included oxygenation failure (defined as endotracheal intubation), Sequential Organ Failure Assessment score on day 3,[19] ICU-acquired infections, mechanical ventilation duration, and ICU lengths of stay. Although it was not a prespecified outcome, we analyzed hospital length of stay.

The data in the tables and figures were collected prospectively using an electronic case report form.

Statistical Analysis

All analyses were conducted according to a published statistical analysis plan.[13] To detect a decrease in 28-day mortality from 35% in the oxygen group to 20% in the noninvasive ventilation group,[6,10,20,21] using a 2-sided χ^2 test, with the α risk set at .05 and 90% power, we needed 187 patients per group (374 patients total).

A single scheduled interim analysis was performed to assess efficacy after enrollment of 50% of the planned sample size, using a 2-sided, symmetric O'Brien-Fleming design and a 2-sided *P* value of .005. This analysis was reviewed by the independent data and safety monitoring board. It yielded a *P* value of .92, and the trial was therefore continued.

The intent-to-treat approach was used. Continuous variables were described as medians (interquartile ranges [IQRs]) and categorical variables as proportions. The primary outcome was compared between the 2 groups using the χ^2 test.

Survival was estimated using the Kaplan-Meier method with administrative censoring on day 28. The cumulative incidence of intubation (with death without intubation as a competing risk) within each randomized group was estimated using a nonparametric estimator and compared using the Gray test.[22] The proportions of ICU-acquired infections in the 2 groups were compared using the χ^2 test and the day-3 Sequential Organ Failure Assessment scores using the Wilcoxon rank-sum test. Median durations of hospital stay, ICU stay, and mechanical ventilation were estimated in both groups using the Kaplan-Meier estimator and compared using the log-rank test, with discharge alive as the event of interest and death as the censoring event.

We applied the Gail and Simon test to assess quantitative interactions between the study treatment and the underlying condition (malignancy vs other) and severity of acute respiratory failure (baseline oxygen flow rate ≤9 L/min vs >9 L/min).[23] Both variables were used for ran-

Table 1. Patient Characteristics at Randomization

Characteristic	No. (%)	
	Oxygen Alone (n = 183)	Noninvasive Ventilation (n = 191)
Age, median (IQR), y	64 (53-72)	61 (52-70)
Men	105 (57.4)	117 (61.3)
Underlying conditions	155 (84.7)	162 (84.8)
Cancer		
Hematologic malignancies	113 (61.7)	125 (65.4)
Solid tumors	42 (23.0)	37 (19.4)
Immunosuppressive drugs	28 (15.3)	29 (15.2)
For non-transplant-related reasons	17 (9.3)	16 (8.4)
After solid organ transplantation	11 (6.0)	13 (6.8)
Chemotherapy at admission	84/155 (54.2)	86/162 (53.1)
Chronic hematologic malignancy	35/155 (22.6)	39/162 (24.1)
Allogeneic stem cell transplantation	29/155 (18.7)	26/162 (16.1)
Remission of the malignancy	19/155 (12.3)	18/162 (11.1)
Comorbidities[a]		
Chronic respiratory insufficiency[b]	12 (6.6)	18 (9.4)
Chronic kidney insufficiency	20 (10.9)	19 (9.9)
Chronic heart insufficiency	10 (5.5)	16 (8.4)
Oxygen flow at ICU admission, median (IQR), L/min	9 (6-15)	8 (6-15)
Time since respiratory symptom onset, median (IQR), d	1 (0-2)	1 (0-2)
Treatment before ICU admission		
Noninvasive ventilation	16 (8.7)	10 (5.2)
Diuretics	47 (25.8)	31 (16.2)
Aerosolized agents	26 (14.3)	19 (9.9)
Anti-infectious agents	138 (75.4)	123 (64.4)
Respiratory parameters at randomization during oxygen therapy, median (IQR)		
Respiratory rate, /min	25 (21-30)	27 (21-31)
Oxygen saturation (Spo_2), %	96 (4-98)	96 (94-98)
Oxygen flow, L/min	9 (6-15)	9 (5-15)
Pao_2:Fio_2 ratio, mm Hg[c]	130 (86-205)	156 (95-248)
SOFA score at randomization, median (IQR)[d]	5 (3-7)	5 (3-7)

Abbreviations: Fio_2, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment score; Spo_2, peripheral capillary oxygen saturation.

[a] Described using the Charlson Comorbidity Index.

[b] Chronic respiratory insufficiency includes obstructive or restrictive chronic respiratory diseases.

[c] Fio_2 was estimated according to the scale used in (ref jama JL Vincent).

[d] SOFA score collects information on the presence and the intensity of respiratory, coagulation, hemodynamic, neurologic, liver, and kidney failure. Each organ is assessed from 0 (no failure) to 4 (worse failure). The worse value was assessed each day.

domization stratification. We conducted exploratory analyses of the primary outcome in subgroups defined by these 2 variables, building logistic regression models to compare odds ratios for death within 28 days, with their 95% confidence intervals.

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

Results

Patients

Of the 374 included patients, 191 were randomly assigned to the early noninvasive ventilation group and 183 to the oxygen therapy alone group (**Figure 1**). No patient was lost to follow-up. Baseline characteristics were evenly distributed between the 2 groups (**Table 1**). All patients received standard oxygen at randomization, with oxygen flows and ratios of Pao_2 to fraction of inspired oxygen (Fio_2) suggesting moderate to severe hypoxemia.

Acute leukemia and aggressive lymphoma were the most common hematologic malignancies, lung cancer the most common solid tumor, and kidney the most common solid organ transplant. Underlying immunosuppression included hematologic malignancies (n = 238 [63.6%], chiefly acute leukemia and aggressive lymphoma), solid tumors (n = 79 [21.1%], chiefly lung cancer), drug-related immunosuppression (n = 33 [8.8%]), and solid organ transplants (n = 24 [6.4%], chiefly kidney transplants).

The cause of acute respiratory failure was infectious for two-thirds of patients (**Table 2**) and unknown for 17 patients.

Interventions

All patients in the noninvasive ventilation group received noninvasive ventilation immediately after randomization. Median durations of noninvasive ventilation were 8 (IQR, 4-11) hours within the first 24 hours, 6 (IQR, 4-8) hours on day 2, and 5 (IQR, 3-7) hours on day 3. Fourteen patients (7.3%) received only a single session of noninvasive ventilation, 5 because they were subsequently intubated and 9 because they could not tolerate noninvasive ventilation; of these 9 patients, none was intubated and all survived. In the oxygen group, 3 patients (1.5%) received rescue noninvasive ventilation (including 2 who were eventually intubated). High-flow nasal oxygen was given to 141 patients overall (37.7%) and was used more often in the oxygen group (44.3%) than in the noninvasive ventilation group (31.4%) ($P = .01$).

As shown in Table 2, there were 142 patients who underwent bronchoscopy and bronchoalveolar lavage, with no significant difference between the 2 groups. During the ICU stay, vasopressors were needed for 148 patients (39.7%) and renal replacement therapy for 58 patients (15.5%), with no significant difference between groups.

Physiological and Laboratory Values

Oxygen saturation and respiratory rate over the 12 hours after randomization were not significantly different between the 2 groups (eFigure 1 in Supplement 2). Median Pao_2:Fio_2 ratios were 156 (IQR, 100-237) mm Hg on day 1, 169 (IQR, 108-236) mm Hg on day 2, and 158 (IQR, 108-226) mm Hg on day 3, with no significant between-group difference. The lowest oxygen saturation values and highest respiratory rates over the 3 days after randomization did not differ significantly between the groups (eFigure 2 in Supplement 2). In the noninvasive ventilation group, median expiratory

tidal volumes were 8.8 (IQR, 7.3-11.4) mL/kg of ideal body weight on day 1, 9.1 (IQR, 7.20-10.7) on day 2, and 9.5 (IQR, 7.2-11.8) on day 3, with no significant difference according to noninvasive ventilation success vs failure or between survivors and nonsurvivors.

Primary Outcome

On day 28 after randomization, the primary outcome (death from any cause) had occurred in 46 of 191 patients (24.1%) in the noninvasive ventilation group and 50 of 183 patients (27.3%) in the oxygen alone group (P = .47) (**Table 3**, **Figure 2**, and **Figure 3**). The absolute difference in day-28 mortality with noninvasive ventilation compared with oxygen alone was −3.2% (95% CI, −12.1% to 5.6%). Survival time did not differ significantly between the groups (Figure 2), and no interactions of the intervention effect with the predefined subgroups were demonstrated (Figure 3).

Secondary Outcomes

The proportion of patients requiring intubation was 41.4% (n = 155) overall, 38.2% (n = 73) in the noninvasive ventilation group, and 44.8% (n = 82) in the oxygen alone group (absolute difference, −6.6 [95% CI, −16.6 to 3.4]; P = .20). Time to intubation was not significantly different in the 2 groups (**Figure 4**). None of the other secondary outcomes differed significantly between the groups (Table 3).

Post Hoc Outcomes

Comparison of Randomized Groups

ICU mortality was 20.9% with noninvasive ventilation and 24.6% with oxygen alone; corresponding values for hospital mortality were 30.9% and 34.4%. Median hospital length of

Table 2. Diagnostic Strategies and Identified Causes of Acute Respiratory Failure

	No. (%)	
	Oxygen Alone (n = 183)	Noninvasive Ventilation (n = 191)
Noninvasive diagnostic tests	163 (89.1)	163 (85.3)
Bronchoscopy and bronchoalveolar lavage	78 (42.6)	64 (33.9)
Causes[a]		
Bacterial pneumonia[b]	83 (45.6)	87 (45.5)
Pneumocystis jirovecii pneumonia	21 (11.5)	22 (11.5)
Viral pneumonia	15 (8.2)	19 (9.9)
Lung involvement by the underlying disease	15 (8.2)	21 (11)
Drug-related pulmonary toxicity	9 (4.9)	10 (5.2)
Invasive pulmonary aspergillosis	4 (2.2)	6 (3.1)
Cardiogenic pulmonary edema	2 (1.1)	7 (3.6)
ARDS (extrapulmonary causes)	12 (6.6)	11 (5.6)
Diffuse intra-alveolar hemorrhage	2 (1.1)	0 (0)
Other identified causes[c]	9 (4.9)	2 (2.1)
No identified cause	11 (6)	6 (4.2)

Abbreviation: ARDS, acute respiratory distress syndrome.

[a] Primary etiological diagnoses established by the investigators based on predefined criteria.[11] In 29 patients, there was an associated pulmonary condition that was either less acute (eg, previously known pulmonary involvement by the underlying disease) or not directly responsible for the acute respiratory failure that required ICU admission (eg, associated viral infection, bronchiectasis, or chronic radiation pneumonitis).

[b] Bacterial pneumonia was defined as pneumonia documented clinically or microbiologically based on predefined criteria.[11] Among these, 5 experienced an exacerbation during neutropenia recovery.

[c] Large pleural effusions (n = 4), pulmonary infarction revealing pulmonary embolism (n = 5), disseminated toxoplasmosis (n = 1), and pain-related atelectasis (n = 1).

Table 3. Primary and Secondary End Points

	Oxygen Alone (n = 183)	Noninvasive Ventilation (n = 191)	Absolute Difference (95% CI)	*P* Value
Primary End Point				
All cause 28-d mortality, No. (%)	50 (27.3)	46 (24.1)	−3.2 (−12.1 to 5.6)	.47
Secondary End Points				
Need for invasive mechanical ventilation, No. (%)	82 (44.8)	73 (38.2)	−6.6 (−16.6 to 3.4)	.20
SOFA on day 3, median (IQR)	4 (2-6)	4 (2-5)	−0.5 (−1.2 to 0.3)	.17
ICU-acquired infection, No. (%)	46 (25.1)	48 (25.1)	0 (−8.8 to 8.8)	.99
Length of ICU stay, median (IQR), d	7 (3-16)	6 (3-16)	−0.3 (−3.2 to 2.6)	.55
Duration of mechanical ventilation, median (IQR), d	14 (6-33)	17 (6-38)	0.3 (−5.7 to 6.3)	.70
Length of hospital stay, median (IQR), d	22 (14-42)	24 (12-43)	0.3 (−5 to 5.5)	.99
Mortality at 6 mo, No. (%)[a]	82/181 (45.3)	72/182 (39.6)	−5.7 (−16.4 to 3.9)	.23
Good performance status in 6-mo survivors, No. (%)[b]	70/75 (93.3)	85/91 (93.4)	−0.1 (−7.7 to 7.5)	.98

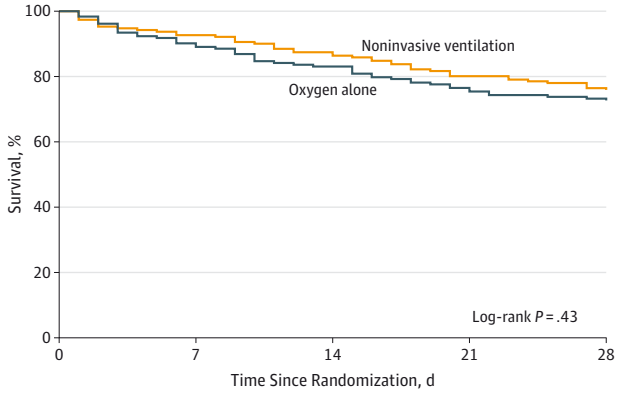
Abbreviations: ICU, intensive care unit; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment score.

[a] Lost to follow-up: n = 2 (oxygen group), n = 9 (noninvasive ventilation group).

[b] Missing data: n = 24 (oxygen group), n = 19 (noninvasive ventilation group).

Need for mechanical ventilation was based on clinical response to oxygen or noninvasive ventilation, clinical status (including peripheral capillary oxygen saturation (Spo_2), respiratory rate, signs of respiratory distress, and bronchial secretion volume), and patient's adherence to noninvasive ventilation. Criteria for mechanical ventilation were severe hemodynamic instability (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 (Spo2 < 92% or respiratory rate >40/min regardless of the oxygen flow rate or use of accessory muscles of respiration), inability to maintain Pao_2 greater than 65 mm Hg with fraction of inspired oxygen greater than 0.6 or dependency on noninvasive ventilation with inability to remain off noninvasive ventilation for longer than 2 h, 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)

Figure 2. Probability of Survival at Day 28

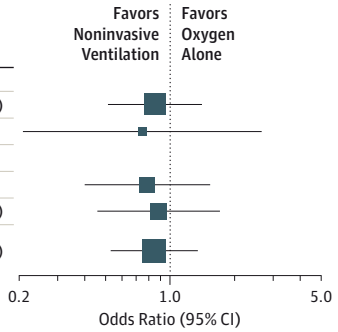


No. at risk					
Noninvasive ventilation	191	177	167	153	146
Oxygen alone	183	165	152	140	134

Probability of survival and subgroup analyses of the risk of day-28 mortality Kaplan-Meier estimates of the probability of day-28 mortality in immunocompromised patients with acute respiratory failure receiving either early noninvasive ventilation or oxygen only. Statistical test used the log-rank test.

Figure 3. Odds Ratio for 28-Day Mortality in the Early Noninvasive Ventilation Group, Compared With the Oxygen Group, Overall and in Predefined Subgroups

Source	No. of Deaths/Total No.		Odds Ratio (95% CI)	P Value for Interaction[a]
	Oxygen Alone	Noninvasive Ventilation		
Underlying Conditions				
Solid tumors or hematologic malignancies	43/150	41/161	0.85 (0.51-1.40)	.66
Immunosuppressive treatment or organ transplant	7/33	5/30	0.74 (0.2-2.63)	
Oxygen flow at randomization[b]				
>9 L/min	26/77	24/84	0.78 (0.4-1.53)	.64
≤9 L/min	24/106	22/107	0.88 (0.46-1.70)	
All patients	50/183	46/191	0.84 (0.53-1.34)	



Underlying conditions were those mentioned by investigators at randomization. These may have been changed after further validation and thus differ from those in Table 1, which includes the final underlying immunosuppressive conditions . Sizes of data markers correspond to the relative size of each subgroup. Error bars indicate 95% confidence intervals.

[a] From the Gray test.

[b] Dichotomization at 9 L/min was preplanned and represents a subgroup from stratification.

stay was not different between the 2 groups (24 [IQR, 12-43] days in the noninvasive ventilation group vs 22 [IQR, 14-42] days in the oxygen alone group, P = .99). Day-28 mortality was 27.0% among cancer patients and 19.0% among patients with immunosuppressive treatments for organ transplantation or other reasons (P = .19). Comparing patients receiving oxygen at 9 L/min or less vs more than 9 L/min at randomization showed day-28 mortality rates of 26.1% and 31.1%, respectively (P = .03). No patient experienced cardiac arrest during intubation.

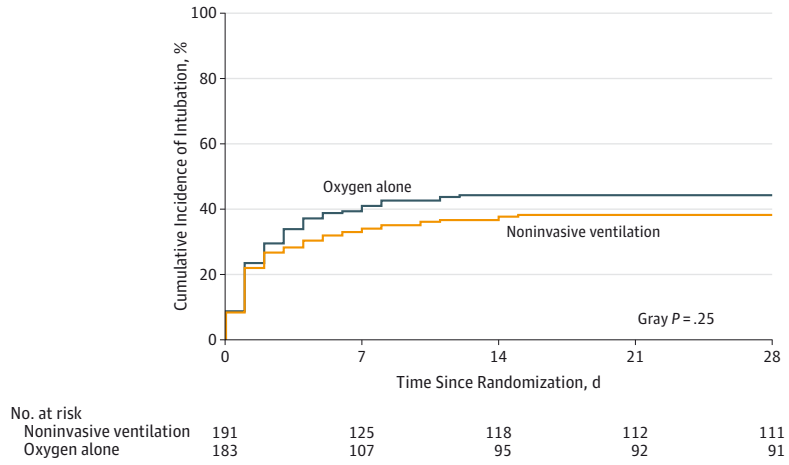
Nonrandomized Comparisons

Among patients who died within 28 days after randomization, 19 died after ICU discharge, followed by a treatment-limitation decision made on the ward (8 in the noninvasive ventilation group and 11 in the oxygen group). Among intubated patients, day-28 mortality was 49.7% (77/155), with no significant difference between the groups (52.1% with noninvasive ventilation and 47.6% with oxygen alone, P = .58) or according to time from randomization to intubation. Of the 141 patients given high-flow nasal oxygen, 15 of 60 (25.4%) died in the noninvasive ventilation group, vs 26 of 81 (32.1%) in the oxygen group (P = .36).

Discussion

In this multicenter randomized trial enrolling critically ill immunocompromised patients with acute respiratory failure, early noninvasive ventilation, compared with oxygen therapy alone, did not reduce the primary outcome of day-28 all-cause mortality, either overall or in any of the prespecified subgroups. There were no significant differences in the proportions of patients who required intuba-

Figure 4. Cumulative Incidence of Intubation Throughout the 28 Days



Cumulative incidence of intubation throughout the 28 days after randomization in immunocompromised patients with acute respiratory failure receiving either early noninvasive ventilation or oxygen only.

tion, in ICU or hospital lengths of stay, or in duration of invasive mechanical ventilation.

The lack of survival benefits from noninvasive ventilation in our study is probably ascribable to the greater than 50% decrease in the rates of intubation and mortality compared with earlier work.[7] When planning the study, we assumed a mortality rate of 35% in the oxygen alone group, based on previous studies.[6,10] The observed rate was only 27.3% and was far lower than in earlier studies,[7] in keeping with reports of improved survival of critically ill immunocompromised patients.[5,24] Of note, a multicenter observational study showed similar outcomes after noninvasive ventilation of immunocompromised patients who had no treatment-limitation decisions at ICU admission,[25] as was the case for our patients.

Strengths of our study include the multicenter design and the high adherence to noninvasive ventilation started immediately after randomization. The profile of infectious diseases in our population indicates severe immunologic impairment. Moreover, only 4.5% of patients had acute respiratory failure of unknown cause, a factor known to confound mortality in this setting.[10,14] Also, no patient was lost to follow-up. The statistical analysis plan was published before recruitment was completed, reducing the risk of analytical bias.[13] Although the nature of the study treatments precluded blinding, the risk of bias was minimized by using central randomization, concealment of study-group assignments before randomization to avoid selection bias, and a robust primary outcome that could not be influenced by observer bias. The results also have a high degree of external validity, since the centers belong to a large study group including university and nonuniversity hospitals.[6,10,20,21]

Our inclusion criteria were similar to those used in the previous trial of early noninvasive ventilation in nonpostoperative ICU patients,[7] in which the mortality rates were considerably higher (50% with noninvasive ventilation and 81% with oxygen alone). Acute illness severity and goals of care before randomization were comparable in the 2 studies. We found no evidence that noninvasive ventilation influenced any of the mortality estimates or was beneficial in subgroups defined based on hypoxemia severity or underlying condition. Similarly, most of the recent observational studies showed no survival benefits from noninvasive ventilation in this setting.[9,12,26-29] That tidal volumes during the first 3 days were related neither to success or failure of noninvasive ventilation nor to day-28 mortality does not support an increase in the incidence of ventilation-induced lung injury in the noninvasive ventilation group.[30]

The present study has several limitations. First, the lower than expected mortality rate with oxygen alone limited the power of our study to detect a significant between-group difference in mortality. Therefore, there remains uncertainty regarding our null finding, which may nonetheless fail to exclude a clinically important effect. For instance, for day-28 survival, the lower confidence limit of a 12% superior survival is close to the 15% absolute risk reduction used in the sample size calculation. Similarly, for intubation, the lower confidence limit is 16.6%. Second, high-flow nasal oxygen was used in about two-fifths of our patients and may have served to decrease the intubation and mortality rates.[30] The significantly higher proportion of patients given this treatment modality in the oxygen alone group may have limited our ability to detect an effect of noninvasive ventilation. Studies comparing use of high-flow nasal oxygen vs standard oxygen and noninvasive ventilation for critically ill immunocompromised patients are needed.

Conclusions

Among immunocompromised patients admitted to the ICU with hypoxemic acute respiratory failure, early noninvasive ventilation compared with oxygen therapy alone did not reduce 28-day mortality. However, study power was limited.

ARTICLE INFORMATION

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Author Affiliations: Saint-Louis University Hospital, Paris, France (Lemiale, Chevret, Azoulay); IPC, Lyon, France (Mokart); APHP, Paris, France (Resche-Rigon, Pène, Théodose, Canet, Rabbat, Mariotte, Bouadma, Demoule); Service de Pneumologie Et Réanimation Médicale, AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Paris, France (Mayaux); Hospices Civils de Lyon, Lyon, France (Faucher); Roubaix, Roubaix, France (Nyunga); Medical Intensive Care Unit, Charles Nicolle University Hospital-Rouen University, Rouen, France (Girault); Centre Hospitalier Universitaire-Nancy, Nancy, France (Perez); University Hospital of Nantes, Nantes, France (Guitton); The Institut Gustave-Roussy (IGR), France (Ekpe); Intensive Care Unit, CHRU Angers, Angers, France (Kouatchet); Intensive Care Medicine, Ghent, Gent, Belgium (Benoit); Medical Intensive Care Unit, La Source Hospital-CHR Orleans, Orléans, France (Barbier); Intensive Care Unit, Hopital Andre Mignot-Le Chesnay, Paris, France (Bruneel); Hôpital d'Avicenne, APHP, Bobigny, France (Vincent, Cohen); Lapeyronie University Hospital, Montpellier, France (Klouche); Centre Hospitalier Universitaire-Amiens, Amiens, France (Loay); Centre de Réanimation, CHRU Lille, Lille, France (Moreau); Centre Hospitalier Universitaire-Caen, Caen, France (Seguin); Institut Jules Bordet, Brussels, Belgium (Meert); Réanimation Médicale, Centre Hospitalier Universitaire-Nantes, Nantes, France (Reignier); Réanimation DRIS, Hopital Nord, Marseille, France (Papazian); Centre Hospitalier Sud Francilien (CHSF), France (Mehzari); The Hôpital civil de Strasbourg, Strasbourg, France (Schenck); The Centre Hospitalier Universitaire de Grenoble, Grenoble, France (Hamidfar); Medical-Surgical ICU, Saint-Etienne University Hospital, Saint-Etienne, France (Darmon).

Author Contributions: Drs Lemiale and Resche-Rigon had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Lemiale, Resche-Rigon, Benoit, Rabbat, Vincent, Loay, Demoule, Chevret, Azoulay.
Acquisition, analysis, or interpretation of data: Lemiale, Mokart, Resche-Rigon, Pène, Mayaux, Faucher, Nyunga, Girault, Perez, Guitton, Ekpe, Kouatchet, Théodose, Canet, Barbier, Rabbat, Bruneel, Vincent, Klouche, Mariotte, Bouadma, Moreau, Seguin, Meert, Reignier, Papazian, Mezhari, Cohen, Schenck, Hamidfar, Darmon, Demoule, Chevret, Azoulay.
Drafting of the manuscript: Lemiale, Resche-Rigon, Perez, Ekpe, Théodose, Vincent, Azoulay.
Critical revision of the manuscript for important intellectual content: Lemiale, Mokart, Pène, Mayaux, Faucher, Nyunga, Girault, Guitton, Kouatchet, Benoit, Canet, Barbier, Rabbat, Bruneel, Vincent, Klouche, Loay, Mariotte, Bouadma, Moreau, Seguin, Meert, Reignier, Papazian, Mezhari, Cohen, Schenck, Hamidfar, Darmon, Demoule, Chevret, Azoulay.
Statistical analysis: Lemiale, Rigon, Mayaux, Chevret.
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Study supervision: Lemiale, Mokart, Mayaux, Guitton, Kouatchet, Demoule, Chevret, Azoulay.

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Independent Data and Safety Monitoring Committee: S. Jaber, CHU Montpellier, France; C. E. Luyt, Pitié Salpêtrière Hospital, Paris, France; B. Maitre, Henri Mondor Hospital, Créteil, France.

Data source: The following hospitals have screened and included patients for this trial: *Amiens:* Hopital Nord: K. Loay. *Angers:* Hôpital Larrey: A. Kouatchet. *Bobigny:* Hôpital Avicenne: F. Chemouni, Y. Cohen. *Bruxelles:* Institut J. Bordet: A. P. Meert. *Caen:* Centre Hospitalier côte de Nacre: A. Seguin. *Corbeil:* Hôpital Sud Francilien: G. Choukroun. *Ghent:* Hôpital Universitaire: D. Benoit. *Grenoble:* Hôpital Michallon: R. Hamidfar. *La Roche Sur Yon:* Centre Hospitalier les Oudaries: J. Regnier, G. Colin. *Lille:* Hôpital Calmettes: A. S. Moreau. *Lyon:* Hôpital E. Herriot: L. Argaud, E. Faucher. *Marseille:* Institut Paoli Calmette: D. Mokart. *Marseille:* Hôpital Nord: G. Thomas, L. Papazian. *Nancy:* Hôpital Brabois: P. Perez. *Nantes:* Hôpital Hotel Dieu: C. Guitton, N. Brulé. *Orléans:* Hôpital La Source: F. Barbier. *Montpellier:* Hôpital Lapeyronnie: K. Klouche, D. Daubin. *Paris:* Hôpital Saint Louis: V. Lemiale, E. Azoulay, E. Canet; Hôpital Pitié Salpétrière: J. Mayaux, A. Demoule; Hôpital Cochin: F. Pène, A. Rabbat; Hôpital Bichat: E. Mariotte, L. Bouadma. *Roubaix:* Hôpital Victor Provo: M. Nuynga. *Rouen:* Hôpital Charles Nicolle: C. Girault. *Strasbourg:* Hôpital Hautepierre: M. Schenck. *Saint Etienne:* Hôpital universitaire: M. Darmon. *Villejuif:* Institut Gustave Roussy: K. Ekpe. *Versailles:* Hôpital Mignot: F. Bruneel.

Contributors: This study was performed on behalf of the Groupe de Recherche en Réanimation Respiratoire du patient d'Onco-Hématologie (GRRR-OH): *Amiens:* M. Slama; J. Maizel. *Angers:* Hôpital Larrey: A. Mercat; L. Masson. *Bobigny:* Hôpital Avicenne: F. Chemouni. *Bruxelles:* Institut J. Bordet: A. P. Meert; J. P. Sculier. *Caen:* Centre Hospitalier côte de Nacre: D. du Cheyron. *Corbeil:* Hôpital Sud Francilien: I. Mehzari; M. Gilbert. *Ghent:* Hôpital Universitaire: P. Depuydt. *Grenoble:* Hôpital Michallon: C. Schwebel. *La Roche Sur Yon:* Centre Hospitalier les Oudaries: J. Reignier, G. Colin; J. B. Lascarrou; J. C. Lacherade; M. Henri-Lagarrigue; K. Bachoumas. *Lille:* Hôpital Calmettes: S. Nseir. *Lyon:* Hôpital E. Herriot: E. Faucher. *Marseille:* Institut Paoli Calmette: Y. Pages; Hôpital Nord: G. Thomas, J. M. Forel. *Nancy:* Hôpital Brabois: B. Levy. *Nantes:* Hôpital Hotel Dieu: C. Guitton, C. Agasse; M. Jonas; J. Lober; C. Bretonnière; O. Zambon; L. Nicollet; Morin-Longuet. *Orléans:* Hôpital La Source: A. Mathonnet; T. Boulain; G. Muller. *Montpellier:* Hôpital Lapeyronnie: D. Daubin. *Paris:* Hôpital Saint Louis: E. Canet; D. Reuter; L. Zafrani; B. Schlemmer; Hôpital Pitié Salpétrière: T. Similowski; Hôpital Cochin: F. Daviaud; A. Cariou; G. Geri; N. Marin; A. Lefèbvre; Hôpital Bichat: M. Neuville, J. F. Timsit, M. Wolff. *Rouen:* Hôpital Charles Nicolle: F. Tamion. *Strasbourg:* Hôpital Hautepierre: S. Hatsch; F. Schneider. *Versailles:* Hôpital Mignot: S. Merceron; A. Gros; S. Cavelot.

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