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

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**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%; 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.
The number of patients living with immune deficiencies is increasing steadily. These patients are at high risk for life-threatening complications, especially acute respiratory failure warranting admission to the intensive care unit (ICU). Mortality in this situation has ranged from 40% to 90% and remains high, despite improvements in recent years. Invasive mechanical ventilation strongly predicts mortality, 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 hypoxic 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. Subsequently, use of noninvasive ventilation as a first-line strategy for immunocompromised patients presenting in acute respiratory failure was incorporated into international guidelines. However, this recommendation remains debated, as it was informed primarily by a single small randomized trial in which the control group had a high mortality rate. Moreover, the trial was conducted in 1998-1999, and, since then, outcomes of critically ill immunocompromised patients have improved considerably. Furthermore, failure of noninvasive ventilation followed by delayed intubation may increase mortality.

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 hypoxic 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. 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. Eligibility criteria were 18 years or older; acute hypoxemic respiratory failure (PaO2 <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.

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 to 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
end-expiratory pressure between 2 and 10 cm H₂O. The fraction of inspired oxygen and positive end-expiratory pressure levels were adjusted to maintain the peripheral capillary oxygen saturation (SpO₂) 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, SpO₂, and consciousness were monitored.

In both groups, intubation decisions were based on the therapeutic response, clinical status (including SpO₂, 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. 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, 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. To detect a decrease in 28-day mortality from 35% in the oxygen group to 20% in the noninvasive ventilation group, using a 2-sided χ² test, with the a 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 χ² 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. The proportions of ICU-acquired infections in the 2 groups were compared using the χ² 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). Both variables were used for ran-
Abbreviations: FiO₂, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment score; 95% confidence intervals.

odds ratios for death within 28 days, with their 95% confidence intervals.

odored 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 PaO₂ to fraction of inspired oxygen (FiO₂) 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 PaO₂:FiO₂ 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 stay was 22 (IQR, 14-42) days with noninvasive ventilation and 24 (IQR, 12-43) days with oxygen alone (P = .99). Duration of mechanical ventilation was 14 (IQR, 6-33) days with noninvasive ventilation and 17 (IQR, 6-38) days with oxygen alone (P = .20). Length of ICU stay was 7 (IQR, 3-16) days with noninvasive ventilation and 6 (IQR, 3-16) days with oxygen alone (P = .55). ICU-acquired infection was 25.1% with noninvasive ventilation and 28.7% with oxygen alone (P = .39). Need for invasive mechanical ventilation was 44.8% with noninvasive ventilation and 47.2% with oxygen alone (P = .55).

**Comparison of the Subgroups**

No identified cause 11 (6) 6 (4.2)

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

<table>
<thead>
<tr>
<th>Cause</th>
<th>Oxygen Alone (n = 183)</th>
<th>Noninvasive Ventilation (n = 191)</th>
<th>Absolute Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninvasive diagnostic tests</td>
<td>163 (89.1)</td>
<td>163 (85.3)</td>
<td></td>
<td></td>
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<tr>
<td>Bronchoscopy and bronchoalveolar lavage</td>
<td>78 (42.6)</td>
<td>64 (33.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Causes*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial pneumonia*</td>
<td>83 (45.6)</td>
<td>87 (45.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumocystis jiroveci pneumonia</td>
<td>21 (11.5)</td>
<td>22 (11.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral pneumonia</td>
<td>15 (8.2)</td>
<td>19 (9.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung involvement by the underlying disease</td>
<td>15 (8.2)</td>
<td>21 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-related pulmonary toxicity</td>
<td>9 (4.9)</td>
<td>10 (5.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive pulmonary aspergillosis</td>
<td>4 (2.2)</td>
<td>6 (3.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiogenic pulmonary edema</td>
<td>2 (1.1)</td>
<td>7 (3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARDS (extrapulmonary causes)</td>
<td>12 (6.6)</td>
<td>11 (5.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse intra-alveolar hemorrhage</td>
<td>2 (1.1)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other identified causes*</td>
<td>9 (4.9)</td>
<td>2 (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No identified cause</td>
<td>11 (6)</td>
<td>6 (4.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ARDS, acute respiratory distress syndrome.

* Primary etiological diagnoses established by the investigators based on predefined criteria. 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).

Other identified causes:
- Bacterial pneumonia was defined as pneumonia documented clinically or microbiologically based on predefined criteria. Among these, 5 experienced an exacerbation during neutropenia recovery.
- Large pleural effusions (n = 4), pulmonary infarction revealing pulmonary embolism (n = 5), disseminated toxoplasmosis (n = 1), and pain-related atelectasis (n = 1).
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 intubation.
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.
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