NON-INVASIVE VENTILATION FOR IMMUNOCOMPROMISED PATIENTS WITH ACUTE RESPIRATORY FAILURE
I-VNICTUS STUDY

Groupe de Recherche en Réanimation Respiratoire du patient d'Onco-Hématologie (GRRR-OH)
Effect of Noninvasive Ventilation vs Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure: A Randomized Clinical Trial

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Mortality of immunocompromised patients requiring intubation and mechanical ventilation

1990’s
70-90%
- Hilbert
NEJM 2001
- Azoulay
CCM 2001
- Azoulay
Medicine 2004

2010’s
40-60%
- Azoulay
AJRCCM 2010
- Shellongowski
Hematologica 2011
- Gristina
CCM 2011
- Mokart
ERJ 2012
- Azoulay
JCO 2013
Impact of NIV 2001 vs. 2013

2001: mortality of intubated patients: 87%

2013: mortality of intubated patients: 60%

1. Less events in 2013 as compared to 2001
2. Less impact of NIV

Hilbert et al.

Lemiale et al.
Impact of NIV on mortality

- Antonelli\(^8\) (20/20) OR=0.44 [0.12 – 1.57]
- Hilbert\(^{12}\) (26/26) OR=0.24 [0.07 – 0.82]
- Azoulay\(^{20}\) (124/79) OR=2.02 [1.13 – 3.61]
- Depuydt\(^{21}\) (113/24) OR=1.52 [0.56 – 4.14]
- Azoulay\(^{13}\) (82/137) OR=1.50 [0.84 – 2.65]
- Gristina\(^{23}\) (1028/274) OR=0.68 [0.52 – 0.89]

Summary OR=0.94 [0.53 – 1.65]
The iVNICTUS trial

- Multicenter randomized controlled trial

- To test the hypothesis that early NIV, compared to oxygen only, decreased all-cause day-28 mortality in immunocompromised patients admitted to the ICU with hypoxemic acute respiratory failure.
Inclusion criteria

- Age ≥ 18 years

**Immune deficiency:**
- Hematological malignancy or solid tumor
- or Solid organ transplant
- or Long term (>30 days) or high dose (>1mg/kg/j) steroids
- or Immunosuppressive drugs

**Acute hypoxemic respiratory failure without intubation criteria**
- PaO2<60mmHg on room air
- or Tachypnea>30/min
- or Labored breathing or respiratory distress or dypnea at rest
Exclusion criteria

- Contraindications to NIV.
- Hypercapnia over 50 mmHg.
- Acute pulmonary oedema
- Need for immediate invasive mechanical ventilation
- Need for epinephrine or norepinephrine >0.3µg/Kg/min
- Ongoing myocardial infarction or acute coronary syndrome
- Impaired consciousness (Glasgow Coma Scale <13)
- Do-not intubate decision
- Long term oxygen therapy
- Pregnancy or breastfeeding
- Absence of coverage by the French statutory health insurance system
Study design and intervention

Baseline Patient ARF

Clinical datas
Intubation criteria
NIV/Oxygen
SOFA score

Mortality

Experimental group: early NIV + O₂

Control group: O₂ alone

Randomisation

H₀ D₁ D₂ D₃ D₄ D₅ D₆ D₇-D₁₄ D₂₈ D₁₈₀
Study outcomes

• Primary endpoint: All cause Day-28 mortality

• Secondary endpoints:
  • Need of mechanical ventilation
  • Comfort
  • SOFA at D3
  • Length of mechanical ventilation, ICU stay and hospital stay
  • ICU-acquired infection rate
  • Performance status at day 180
Statistical analysis

• Analyses conducted according to a previously published statistical analysis plan.

• To detect a decrease in 28-day mortality from 35% in the oxygen group to 20% in the NIV group, 187 patients are needed per group (374 in all).

• Intent-to-treat analysis
680 met all study inclusion criteria

306 were not included
- 81 met ≥1 exclusion criterion
- 82 required immediate intubation
- 55 had do-not-intubate orders
- 33 declined participation
- 19 were eligible but were not randomized
- 10 were outside randomization window
- 9 were previously included into the study
- 17 had other reasons

374 were randomized

183 were assigned to oxygen therapy only
- Three (1.5%) patients received rescue noninvasive ventilation

191 were assigned to Non-invasive ventilation
- All patients received NIV
  - 14 (7.3%) received a single NIV session

183 were included in the intent-to-treat analysis of the primary outcome

191 were included in the intent-to-treat analysis of the primary outcome
# Patient’s characteristics

<table>
<thead>
<tr>
<th></th>
<th>Oxygen group (N=183)</th>
<th>NIV group (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>64 [53-72]</td>
<td>61 [52-70]</td>
</tr>
<tr>
<td><strong>Gender (male)</strong></td>
<td>105 (57.4)</td>
<td>117 (61.3)</td>
</tr>
<tr>
<td><strong>Underlying conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>155 (84.7)</td>
<td>162 (84.8)</td>
</tr>
<tr>
<td>Immunosuppressive drug</td>
<td>28 (15.3)</td>
<td>29 (15.2)</td>
</tr>
<tr>
<td><strong>Oxygen flow at ICU admission (L/min)</strong></td>
<td>9 [6-15]</td>
<td>8 [6-15]</td>
</tr>
<tr>
<td><strong>Time (days) since respiratory-symptom onset</strong></td>
<td>1 [0-2]</td>
<td>1 [0-2]</td>
</tr>
<tr>
<td><strong>Respiratory parameters at randomization during oxygen therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate (/min)</td>
<td>25 [21-30]</td>
<td>27 [21-31]</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>96 [4-98]</td>
<td>96 [94-98]</td>
</tr>
<tr>
<td>Oxygen flow (L/min)</td>
<td>9 [6-15]</td>
<td>9 [5-15]</td>
</tr>
<tr>
<td>PaO2/FiO2 ratio*</td>
<td>130 [86-205]</td>
<td>156 [95-248]</td>
</tr>
<tr>
<td><strong>SOFA score</strong></td>
<td>5 [3-7]</td>
<td>5 [3-7]</td>
</tr>
</tbody>
</table>
PaO$_2$/FiO$_2$

Oxygen group

NIV group

NS

D1

n=148

n=75

D2

n=102

n=46

D3

n=69

n=20

Oxygen group

NIV group
Maximum respiratory rate

Respiratory Rate (/min)

<table>
<thead>
<tr>
<th></th>
<th>NS</th>
<th>NS</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D1</td>
<td>D2</td>
<td>D3</td>
</tr>
<tr>
<td>n</td>
<td>178</td>
<td>141</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td>184</td>
<td>149</td>
<td>118</td>
</tr>
</tbody>
</table>
Primary outcome: 28-day mortality

- Oxygen group (28-day mortality 27.3%)
- NIV group (28-day mortality 24.1%)

p-value = 0.43
28-day mortality in predefined subgroups

All patients (N=374)
- Mortality: Oxygen 50/183, NIV 46/191
- Odds Ratio (95% CI): 0.84 (0.53–1.34)

Underlying Conditions
- Solid tumors or hematological malignancies
  - Mortality: Oxygen 43/150, NIV 41/161
  - Odds Ratio (95% CI): 0.85 (0.51–1.40)
- IS treatment or organ transplant
  - Mortality: Oxygen 7/33, NIV 5/30
  - Odds Ratio (95% CI): 0.74 (0.2–2.63) P = 0.66

Oxygen requirement at randomization
- O2 > 9l/min
  - Mortality: Oxygen 26/77, NIV 24/84
  - Odds Ratio (95% CI): 0.78 (0.4–1.53) P = 0.64
- O2 ≤ 9l/min
  - Mortality: Oxygen 24/106, NIV 22/107
  - Odds Ratio (95% CI): 0.88 (0.46–1.70)
Secondary outcome Intubation rate

- Oxygen group: 38.2%
- NIV group: 44.8%

Gray test, p.value = 0.25

Time (days) since randomization

Cumulative incidence of intubation

Patients at risk

Oxygen group
NIV group
# Secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>Oxygen group (N=183)</th>
<th>NIV group (N=191)</th>
<th>Absolute Difference 95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFA on day 3</td>
<td>4 [2-6]</td>
<td>4 [2-5]</td>
<td>-0.5 (-1.2, 0.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>ICU-acquired infection</td>
<td>46 (25.1)</td>
<td>48 (25.1)</td>
<td>(-8.8, 8.8)</td>
<td>0.99</td>
</tr>
<tr>
<td>Length of ICU stay</td>
<td>7 [3-16]</td>
<td>6 [3-16]</td>
<td>-0.3 (-3.2, 2.6)</td>
<td>0.55</td>
</tr>
<tr>
<td>Duration of mechanical ventilation</td>
<td>14 [6-33]</td>
<td>17 [6-38]</td>
<td>0.3 (-5.7, 6.3)</td>
<td>0.70</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>22 [14-42]</td>
<td>24 [12-43]</td>
<td>0.3 (-5,5.5)</td>
<td>0.99</td>
</tr>
<tr>
<td>Mortality at 6 months*</td>
<td>82 (45.8)</td>
<td>72 (39.6)</td>
<td>-6.2 (-16.4,3,9)</td>
<td>0.23</td>
</tr>
<tr>
<td>Performans status &lt;2 among alive patient**</td>
<td>70/75</td>
<td>85/91</td>
<td>-0.1 (-7.7, 7.5)</td>
<td>0.98</td>
</tr>
</tbody>
</table>
Patients treated with high flow oxygen

• 141 patients received high-flow oxygen,
  • 60 (32%) patients in NIV group
  • 81 (44%) patients in oxygen group

• Mortality was
  • 15/60 (25.4%) died in the NIV group and
    26/81 (32.1%) in the oxygen group
  • (P=0.36)

• HIGH trial ongoing in our study group
Conclusion

- Early NIV, compared with oxygen, did not reduce mortality among critically ill immunocompromized patients with hypoxemic acute respiratory failure.

- However, study power was limited.

- These findings undermine the basis for existing NIV recommendations.
Thank you to participating centers

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Thank you for your attention
Reserve: Tidal volume in NIV group

Tidal volume of body weight (ml/kg)

D1: n=125
D2: n=94
D3: n=47