



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



# Intubation to Nowhere in COVID-19: Can Noninvasive Ventilation Help?

See also page 31

Coronavirus disease 2019 (COVID-19) is associated with multifocal pneumonia and acute respiratory distress syndrome (ARDS) leading to acute hypoxemic respiratory failure. Aside from COVID-19–directed therapy that may include antiviral and immunomodulator agents,<sup>1</sup> respiratory support to maintain oxygen saturation greater than 90% is the mainstay of treatment which spans from low-flow supplemental oxygen, high-flow nasal oxygen (HFNO), continuous positive airway pressure (CPAP) with or without a helmet, noninvasive ventilation (NIV) (usually bilevel), invasive mechanical ventilation (IMV), and extracorporeal membrane oxygenation.<sup>2</sup> Prone positioning in spontaneous breathing or after intubation is also widely used as well as various body positions (eg, Rodin’s Thinker<sup>3</sup>). The relatively low rate of co-infection<sup>4</sup> does not support the routine use of antibiotics initially, and therapeutic anticoagulation has not resulted in a greater probability of survival in intensive care unit (ICU) patients.<sup>5</sup>

COVID-19 ARDS, similar to non–COVID-19 ARDS, should be treated preferentially with noninvasive respiratory strategies, especially HFNO, CPAP or NIV, to limit complications inherent to IMV. Criteria for intubation include altered mental status, hemodynamic instability, and severe hypoxemia.<sup>2</sup> The timing of intubation remains debated. In a qualitative analysis of sepsis-related acute respiratory failure,<sup>6</sup> we found that the right time to intubate was not a specific timepoint but more a bandwidth between “too early” and “too late,” influenced by three domains: patient’s values and preferences, provider’s skills and experience, and the strain of the system such as overcapacity or limited resources. This time frame was also influenced by the severity and the trajectory of the respiratory failure.

Severity alone is not sufficient to decide to intubate. In the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) study, a large, multinational, observational study of ARDS,<sup>7</sup> NIV was used at the same rate (15%) irrespective of ARDS severity, even though delaying intubation in more severe cases was associated with worse outcome. To minimize this paradox, some have proposed reassessment of the expired tidal volume after 4 hours of NIV in moderate-to-severe hypoxemia: an expiratory tidal volume greater than 9.5 mL/kg of ideal body weight predicted NIV failure with a sensitivity of 82% and a specificity of 87%.<sup>8</sup> In COVID-19–related acute respiratory failure, the domains influencing the decision to intubate remain true with some variations. The so-called “happy hypoxia” refers to patients with high oxygen demand who do not appear in distress otherwise. Most critical cases of COVID-19 (70% to 90%) who require intubation have subsequent high mortality (40% to 50%) and high morbidity with multiple organ dysfunction. Distinguishing those who would benefit from early intubation remains difficult, and nomogram and scoring systems have been proposed to predict the probability of noninvasive respiratory strategy failure.<sup>9,10</sup> Factors that could modestly reduce the rate of intubation may include self-prone positioning and the early use of CPAP and NIV,<sup>11</sup> although the length of NIV application before ICU admission combined with age have been identified as independent risk factors of in-hospital mortality.<sup>12</sup> There is now an even bigger challenge when most patients have received antiviral and anti-inflammatory therapy, leaving limited options to prevent the progression of the destructive lung disease, and leading sometimes to an intubation to nowhere.

In this issue of *Mayo Clinic Proceedings*, Chacko et al<sup>13</sup> present the results of a prospective study on the use of NIV in a medical ICU of a tertiary university affiliated hospital in South India in patients with COVID-19–related acute respiratory failure enrolled between April 1, 2020, and September 15, 2020. Among all patients admitted to the ICU with confirmed COVID-19, 286 (81.4%) were first initiated on NIV. Only 36.7% of those admitted to the ICU were intubated, either initially or after NIV failure. The time from symptom onset to the ICU admission was approximately 7 days. Two or more comorbidities were frequently observed (57.3%). The distribution of severity of acute respiratory failure was 26.9% with non-ARDS or mild ARDS, 47.6% with moderate ARDS, and 25.5% with severe ARDS. Remdesivir was used in 47.2% and glucocorticoids in 99.7%. No other immunomodulator was administered. Broad spectrum antibiotics were given in 63.2% and therapeutic anticoagulation in 60.4%. Noninvasive ventilation was used if patients had a respiratory rate greater than 24/min and/or increased work of breathing with accessory muscle, but were otherwise hemodynamically stable, conscious, and cooperative. Dedicated NIV devices were not used; instead, for better oxygen titration and ventilator synchrony, mechanical ventilators were used with a pressure support set up to a target tidal volume around 6 mL/kg ideal body weight and positive end-expiratory pressure and fraction of inspired oxygen (FIO<sub>2</sub>) adjusted to keep oxygen saturation greater than 92%. Awake self-proning was encouraged. Noninvasive ventilation failure was defined as the need to intubate because of respiratory failure that is worsening work of breathing, worsening partial pressure of oxygen (PaO<sub>2</sub>)/FiO<sub>2</sub> (PF) ratio, increased respiratory rate, or altered mental status or hemodynamic instability (patient criteria); the need to intubate was left at the discretion of the clinician (provider criteria) and not limited to logistic considerations (system criteria), despite limited resources with no negative pressure room, limited isolation rooms, and common ICU areas used for

most patients. On follow-up, 28.7% patients failed NIV and required intubation. The overall mortality of those on NIV was 30.1% with an overall median duration time of NIV of 5 days, and for those who failed NIV, a median duration time of IMV of 11 days with a median time to intubation of 4 days. The mortality rate of those never intubated and managed exclusively on NIV was 10.8% yielding an overall success rate of 63.6%, whereas the mortality of those who failed NIV and were intubated was 78%. The mortality of those intubated without ever using NIV was 59.6%. Factors associated with NIV failure and mortality included older age, higher severity score, higher severity of ARDS, and associated multiple organ dysfunction (severity criteria). Patients with no rapid improvement in their PF ratio, or lack of reduction of their respiratory rate (trajectory criteria) had higher risk of NIV failure, and patients with delayed intubation (too-late category) had worse outcome. Among the providers, 3.1% contracted a mild form of COVID-19 infection, despite personal protective equipment.

What can we learn from this study? First, NIV was widely used as a first noninvasive respiratory strategy in the ICU and approximately two-thirds (63.6%) of patients who required NIV were never intubated and survived. This is very similar to the findings in a large cohort in Italy where more than half of those patients survived without the need for intubation.<sup>14</sup> Second, those who failed NIV and required intubation had worse outcome than those who did not, and delayed intubation was more frequent in non-survivors. Third, severity alone was not sufficient to impose intubation even though the rate of NIV failure increased with severity: 16.9% of mild (or non-ARDS), 37.5% of moderate, and 54.8% of severe ARDS eventually required intubation. A lung protective strategy using a mechanical ventilator may have prevented volo- and barotrauma<sup>15</sup> and patient self-induced lung injury,<sup>16</sup> a phenomenon that may be more predominant in intubated patients during the transition from full to partial ventilatory support. Neither CPAP nor HFNO that may

be more protective for the lungs were used as comparator. Alternation in HFNO and CPAP or NIV, especially at night in obese patients, with underlying obstructive sleep apnea, chronic obstructive lung disease, or congestive heart failure was not specified. Fourth, trajectory matters too and, in this study, a rapid improvement in the PF ratio and a greater reduction in the respiratory rate were associated with a higher rate of NIV success. Fifth, the decision to intubate, multifactorial and intrinsically subjective, was left at the discretion of the clinician, without the support of scoring systems. Sixth, this study was complete in mid-September 2020. Since then, COVID-19-directed therapy has evolved with more frequent administration of interleukin 6 inhibitors or Janus kinase inhibitors in combination with glucocorticoids in rapidly progressive respiratory failure to reduce the need for intubation, and therapeutic anticoagulation is not routinely used in the ICU setting. Moreover, the use of high-efficiency particulate air filters on the outlet of NIV circuit, the vaccination of health care workers, and universal masking have mitigated the risks of infection for the care teams and allowed a more freely use of a broader variety of noninvasive respiratory strategies. Finally, the decision to intubate and the optimal timing remain a challenge irrespective of resources. It should be carefully and regularly assessed to balance risk and benefit of both noninvasive and invasive respiratory strategies, ideally in a patient-centered model of care.

**Philippe R. Bauer, MD, PhD**

Division of Pulmonary and Critical Care  
Mayo Clinic  
Rochester, MN

**Potential Competing Interests:** Dr Bauer has received support from AstraZeneca Pharmaceuticals, LP, and Corvus Pharmaceuticals, Inc, for clinical trials, none of which are discussed here.

**Correspondence:** Address to Philippe R. Bauer, MD, PhD, Division of Pulmonary and Critical Care, Mayo Clinic, 200

First Street SW, Rochester, MN 55905, USA (Bauer.Philippe@mayo.edu).

**ORCID**

Philippe R. Bauer:  <https://orcid.org/0000-0001-8429-3581>

**REFERENCES**

1. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. <https://www.covid19treatmentguidelines.nih.gov/>. Accessed October 27, 2021.
2. Nasa P, Azoulay E, Khanna AK, et al. Expert consensus statements for the management of COVID-19-related acute respiratory failure using a Delphi method. *Crit Care*. 2021;25(1):106.
3. Coppo A, Winterton D, Benini A, et al. Rodin's Thinker: an alternative position in awake patients with COVID-19. *Am J Respir Crit Care Med*. 2021;204(6):728-730.
4. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. *J Infect*. 2020;81(2):266-275.
5. REMAP-CAP Investigators; ACTIV-4a Investigators; ATTACC Investigators, et al. Therapeutic anticoagulation with heparin in critically ill patients with COVID-19. *N Engl J Med*. 2021; 385(9):777-789.
6. Bauer PR, Kumbamu A, Wilson ME, et al. Timing of intubation in acute respiratory failure associated with sepsis: a mixed methods study. *Mayo Clin Proc*. 2017;92(10):1502-1510.
7. Bellani G, Laffey JG, Pham T, et al. Noninvasive ventilation of patients with acute respiratory distress syndrome: insights from the LUNG SAFE study. *Am J Respir Crit Care Med*. 2017;195(1):67-77.
8. Carreaux G, Millán-Guilarte T, De Prost N, et al. Failure of noninvasive ventilation for de novo acute hypoxemic respiratory failure: role of tidal volume. *Crit Care Med*. 2016;44(2): 282-290.
9. Liu L, Xie J, Wu W, et al. A simple nomogram for predicting failure of non-invasive respiratory strategies in adults with COVID-19: a retrospective multicentre study. *Lancet Digit Health*. 2021;3(3):e166-e174.
10. Camillo A, Lopez A, Camillo L, et al. Validity of a clinical scale in predicting the failure of non-invasive ventilation in hypoxemic patients. *J Crit Care*. 2020;60:152-158.
11. Cardona S, Downing J, Alfalasi R, et al. Intubation rate of patients with hypoxia due to COVID-19 treated with awake proning: a meta-analysis. *Am J Emerg Med*. 2021;43:88-96.
12. Boscolo A, Pasin L, Sella N, et al. Outcomes of COVID-19 patients intubated after failure of non-invasive ventilation: a multicenter observational study. *Sci Rep*. 2021;11:17730. <https://doi.org/10.1038/s41598-021-96762-1>. Accessed October 28, 2021.
13. Chacko B, Thomas L, Sharma R, et al. *Non-invasive ventilation in the management of respiratory failure due to COVID-19*. Mayo Clin Proc; 2021.
14. Bertaina M, Nuñez-Gil JJ, Franchin L, et al. HOPE COVID-19 investigators. Non-invasive ventilation for SARS-CoV-2 acute respiratory failure: a subanalysis from the HOPE COVID-19 registry. *Emerg Med J*. 2021;38(5):359-365.
15. Tucci MR, Costa EL, Nakamura MA, Morais CC. Noninvasive ventilation for acute respiratory distress syndrome: the importance of ventilator settings. *J Thorac Dis*. 2016;8(9):E982-E986.
16. Gattinoni L, Gattarello S, Steinberg I, et al. COVID-19 pneumonia: pathophysiology and management. *Eur Respir Rev*. 2021;30(162):210138.