
The Changing Landscape of Noninvasive Ventilation in the Intensive Care Unit

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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. Immuno-compromised patients with acute hypoxic 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 [FIO2]). 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, venous thromboembolism, delirium, and cognitive dysfunction. As such, these patients typically have a high associated mortality, estimated at approximately 50%. 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 and acute cardiogenic pulmonary edema. The benefits of noninvasive ventilation in hypoxic 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. 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.

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, 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 FIO2 that could be delivered was typically limited to 30% to 40%. Such ventilators were of limited utility in the care of patients requiring higher FIO2 levels. In addition, the ventilator interface was a rubber face mask that was often prone to air leakage when high pressures were needed. 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 FIO2 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.

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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 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.\(^3\) 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\(^7\) and Antonelli et al\(^8\) 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\(_2\)O 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.

REFERENCES
Mortality Trends and Signs of Health Progress in the United States
Improving Understanding and Action

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In life, death is the ending point. In much of biomedical science and health policy, death is often the starting point. As the saying goes, the finality of death tends to focus the mind—as it does the attention of policy makers and resource allocation. Although health progress depends on understanding and action far beyond that singular event, concise and reliable information about death as a touchstone reference point is necessary, but is not sufficient.

In this issue of JAMA, Ma and colleagues1 contribute important data to help advance understanding of death rates in the United States and the progress reflected in the trends. Their comprehensive assessment of the mortality component of vital statistics data from 1969 to 2013 offers valuable insights on the trends over nearly half a century in deaths from all causes, as well as for 6 leading causes of death. During that period, age-standardized death rate per 100 000 for all causes decreased by 42.9% (from 1278.8 to 729.8), with the most substantial relative reduction in deaths from stroke (down 77%, from 156.8 to 36.0) and heart disease (down 67.5%, from 520.4 to 169.1). Impressive declines were also documented in mortality from unintentional injuries (down 39.8%, from 65.1 to 39.2), cancer (down 17.9%, from 198.6 to 163.1), and diabetes (down 16.5%, from 25.3 to 21.1). On the other hand, the authors report that the death rate for chronic obstructive pulmonary disease (COPD) doubled (from 21.0 to 42.2) in that period.

Although death may be the most definitive marker in health and health care, the need for clear insights on the age of onset, severity, and duration of illness and injury take on greater significance as the population grows older. The authors also contribute on this dimension, reporting that deaths occurring at earlier ages—indicated as age-standardized years of potential life lost before age 75 years—also declined by 52.4% from 1969 to 2013 (from 134.7 to 64.1), with the largest declines, again, occurring for stroke (down 74.8%, from 6.0 to 1.5), heart disease (down 68.3%, from 28.8 to 9.1), unintentional injuries (down 47.5%, from 19.9 to 10.4), and cancers (down 40.6%, from 21.4 to 12.7). Years of potential life lost also declined by 14.5% for diabetes (from 1.9 to 1.6) and were unchanged, overall, for COPD, declining slightly in the most recent time period. The authors note that, as expected, there has been a lag in the decline in years of potential life lost for COPD as smoking rates have declined, and also that diabetes deaths have recently increased, associated with increases in obesity prevalence among adults.

On the other hand, for the purposes of strategic health priorities, health policy initiatives, and optimal core data system capacity to provide the guidance needed, important implicit messages are inherent in what Ma et al were not able to report from their assessment of the data available from the nation’s vital statistics over this period; eg, the trends and outcomes related to basic health challenges such as dementia, mental health, human immunodeficiency virus (HIV)/AIDS, health disparities, as well as those related to the various factors identified as knowledge deepens about the etiologic and potentiating elements involved in these conditions.

For example, in terms of rapidly emerging challenges, Alzheimer disease, with a greater than two-thirds increase in deaths from 2000 to 2013, moved from the eighth to the sixth leading cause of death in that period, but comparable data are not available back to 1969 for the condition.2,4 Suicide increased by a third from 2000 to 2013, highlighting the importance of mental health and depression as prominent health challenges not reflected in the earlier data.3,4 Human immunodeficiency virus became a prominent national and global health concern in the 1980s and 1990s, ranking at one point as high as the eighth leading cause of death, but was not recognized in 1969 and is no longer among the top 10 causes of death. Deaths from HIV/AIDS in the United States have declined from more than 50 000 in 1995 to about 7000 in 2013.4,5


