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Noninvasive Ventilation for Immunocompromised Patients

IMMUNOCOMPROMISED patients with respiratory failure who require mechanical ventilation have notoriously poor prognoses, with mortality rates ranging from 60 to 100 percent, depending on the underlying diagnosis and factors such as age, functional status, the Acute Physiology and Chronic Health Evaluation score, the presence or absence of multiorgan failure, and the duration of neutropenia.[1] Such patients' immunosuppression is most often a consequence of therapy for hematologic cancers, organ transplantation, the acquired immunodeficiency syndrome, or long-term treatment with high doses of corticosteroids. They usually die either from underlying illness or its complications or from the complications of mechanical ventilation.

Although the incidence of and rate of death from *Pneumocystis carinii* pneumonia appear to be dropping among patients infected with the human immunodeficiency virus, probably because of the efficacy of antiretroviral and prophylactic therapy,[2] this has not been the case for patients who require mechanical ventilation after bone marrow transplantation. In one survey of 979 such patients, only 4.7 percent left the hospital alive.[1] Traditionally, immunocompromised patients have undergone endotracheal intubation when their respiratory failure becomes severe. Too often, this intervention has been followed by further, ultimately fatal complications, including pneumonia and sepsis. Clearly, new therapeutic approaches are needed.

In this issue of the *Journal,* Hilbert et al.[3] report on the use of noninvasive mechanical ventilatory assistance delivered through a face mask in immunocompromised patients in whom respiratory failure develops. Consistent with their hypothesis, they found in this randomized study that only 12 of the 26 patients in the noninvasive-ventilation group (46 percent) required intubation, as compared with 20 of the 26 patients (77 percent) who received standard treatment without mechanical ventilation ($P=0.03$). In addition, noninvasive ventilation resulted in a significantly lower rate of serious complications (50 percent, as compared with 81 percent in the standard-treatment group; $P<0.02$) and of death in the hospital (50 percent vs. 81 percent, $P=0.02$). Although not statistically significant, the strongest trends among reductions in individual complications were for ventilator-associated pneumonia, sinusitis, and sepsis. Most of the patients in the study had hematologic cancers with neutropenia and would be expected to have a low rate of survival, so these results are striking and argue strongly for the use of noninvasive ventilation as an initial approach to assisted ventilation in such patients.

The use of noninvasive ventilation, usually administered through an oronasal or nasal mask, has expanded rapidly in critical care units over the past decade. Previous studies have established noninvasive ventilation as the ventilatory mode of choice in selected patients with respiratory failure caused by exacerbations of chronic obstructive pulmonary disease.[4] Recent studies indicate that the use of noninvasive ventilation can reduce the need for intubation and lower the mortality rate in patients with various causes of hypoxemic respiratory failure,[5] although how to select patients who would most benefit from this approach remains unclear. The study by Hilbert et al. included relatively few patients who had undergone organ transplantation. However, a recent randomized trial of noninvasive ventilation in 40 such patients showed significant differences in the rate of intubation (20 percent, as compared with 70 percent in controls) and the rate of death in the intensive care unit, although the rates of death in the hospital did not differ significantly in the two groups.[6] These findings, combined with those of Hilbert et al., support the recommendation that noninvasive ventilation should be considered the ventilatory mode of choice for selected immunocompromised patients with respira tory failure.

The rationale for such a recommendation is strong. In immunocompromised patients, respiratory failure is usually due to diffuse lung injury from infection or noninfectious processes, which impairs gas exchange and produces severe hypoxemia. In such patients, who are often weak and anemic as a result of the underlying illness, ventilation increases in an effort to maintain oxygenation. The demands on the respiratory muscles become excessive, causing fatigue and eventually the retention of carbon dioxide. These events trigger a vicious circle in which deteriorating oxygenation limits the supply of energy to the respiratory muscles, leading to death unless ventilation is supported in some way.

Noninvasive ventilation that combines positive end-expiratory pressure (PEEP) and inspiratory-pressure support interrupts this cycle in several ways. PEEP helps prevent alveolar collapse and improves oxygenation. In addition, the increase in the end-expiratory volume resulting from PEEP shifts respiration to a more compliant portion of the pressure–volume curve, thereby reducing the work of breathing. Finally, if the patient's respiratory efforts are synchronized with those of the ventilator, the inspiratory-pressure support assists inhalation, further reducing the work of breathing. In the end, noninvasive ventilation prevents respiratory muscles from becoming fatigued

and failing and averts the need for intubation, thus lowering the risk of ventilator-associated pneumonia and sepsis,[7] particularly in immunocompromised patients. It is this benefit that presumably explains the reduced rate of death associated with noninvasive ventilation.

A few caveats must accompany the recommendation that noninvasive ventilation be used as the initial mode of mechanical ventilation in immunocompromised patients. The patients in the study by Hilbert et al. were highly selected, and similar selection criteria should be applied in the clinical setting. Noninvasive ventilation was used only in patients with a stable neurologic status who presumably were cooperative and hemodynamically stable without cardiac ischemia or arrhythmias and who did not have acidemia or severe hypercapnia (in this study, they had a partial pressure of arterial carbon dioxide of 55 mm Hg or less). Patients with multiorgan failure or an uncorrected bleeding diathesis were excluded. Although the presence of excessive airway secretions was not listed as a reason for exclusion, it is safe to assume that the authors used this criterion, since the development of copious secretions was a criterion for intubation. The patients required only intermittent ventilatory assistance. It is remarkable that the noninvasive ventilation had so favorable an effect when it was used for an average of only 9 hours during the first 24 hours and 7 hours per 24 hours thereafter. Clearly, these patients did not have severe respiratory failure when noninvasive ventilation was begun.

The timing of the initiation of noninvasive ventilation is important. Hilbert et al. advise early implementation to prevent respiratory failure from progressing. On the other hand, the indiscriminate use of this technique could waste time and resources if patients who do not need ventilatory assistance are treated. As was true in the study by Hilbert et al., patients selected to receive noninvasive ventilation should have severe dyspnea, tachypnea (more than 30 respirations per minute), and hypoxemia (a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of less than 200). The timing of intubation in patients who have no response to noninvasive ventilation is also important. Excessive delay could precipitate a respiratory emergency and increase the risk of serious complications and death.[8] Thus, clinical judgment must be exercised in selecting appropriate patients for noninvasive ventilation, deciding when to initiate it, and determining when intubation is necessary. Good clinical judgment is likely to be rewarded by reduced rates of complications and death.

Continuous positive airway pressure (CPAP) has long been known to improve oxygenation and reduce the work of breathing in patients with acute respiratory failure,[9] raising the possibility that this simpler and less expensive method could be used as effectively as noninvasive ventilation to treat respiratory failure in immunocompromised patients. In a previous prospective but uncontrolled trial, Hilbert et al.[10] found that CPAP alone eliminated the need for intubation in 25 percent of 64 patients with neutropenia. This rate is considerably lower than the 54 percent rate of success of PEEP and pressure support in their current study. A recent randomized trial showed no advantage of noninvasive CPAP over oxygen therapy in immunocompetent patients with hypoxemic respiratory failure.[11] Although there have been no direct comparisons of noninvasive ventilation with noninvasive CPAP in immunocompromised patients, these results suggest that noninvasive ventilation is more effective at averting intubation.

Given the risks of serious complications and death associated with intubation, the relative safety of appropriately applied noninvasive ventilation should change our approach to ventilation in immunocompromised patients with respiratory failure. Patients in whom respiratory distress develops should be treated conventionally with oxygen and other indicated therapies and should be monitored closely. If moderate-to-severe respiratory distress develops with tachypnea and hypoxemia, noninvasive ventilation with PEEP and inspiratory-pressure support should be initiated unless there are contraindications. Only patients who are severely ill or who have no response to noninvasive ventilation should undergo intubation. In fact, considering that none of the patients who required intubation in the study by Hilbert et al. survived to hospital discharge, the question must be raised whether the use of intubation after the failure of noninvasive ventilation is an exercise in futility, at least in the case of patients with hematologic cancers.

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