maintenance oral corticosteroid therapy, and alternative therapeutic approaches might be best, although these are limited for those with no evidence of eosinophilic inflammation.

How can this precision medicine approach be further improved, particularly for those with no evidence of eosinophilic inflammation, to find new treatments? Differential analysis of the omics data characterizing each of these four clusters may provide clues to the pathways that may underlie corticosteroid responsiveness. The other approach would be to first cluster on available transcriptomic or proteomic data. Taking this approach in the U-BIOPRED (Unbiased BIOmarkers in PREDiction of respiratory disease outcomes project) cohort, Kuo and colleagues clustered transcriptomic pathways associated with inflammatory and immune mechanisms in bronchial biopsies and epithelial cells using machine learning to obtain T2-high molecular phenotypes associated with corticosteroid insensitivity (11). With use of an inference scheme, these molecular clusters could be predicted by using the inflammatory biomarkers of sputum eosinophilia and F_{ENO} levels, together with oral corticosteroid use, with good sensitivity and specificity. The work of Wu and colleagues emphasizes the need for the unsupervised approach and the application of machine learning techniques that can provide useful tools for the clinician while improving understanding of corticosteroid insensitivity in severe asthma. ■

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Predicting Outcomes of High-Flow Nasal Cannula for Acute Respiratory Distress Syndrome

An Index that ROX

Noninvasive forms of ventilatory assistance, including noninvasive ventilation (NIV) and high-flow nasal cannula (HFNC), have emerged as important modalities to treat acute respiratory failure during the last 2 decades. NIV use grew rapidly during the decade from 2000 through 2010 (1), when NIV as a proportion of initial ventilator starts in the United States rose as high as 40% (2), and HFNC use has risen during the present decade. According to current guidelines (3), NIV is considered the ventilatory modality of first choice to treat acute hypercapnic respiratory failure in patients with chronic obstructive pulmonary disease, as well as cardiogenic pulmonary edema. NIV has not been so successful in patients with *de novo* hypoxemic respiratory failure resulting from pneumonia/acute respiratory distress syndrome (ARDS), with intubation rates as high as 50–66% (2, 4) and with particularly high mortality rates in these NIV failures (5). The European Respiratory Society/American Thoracic Society guideline on NIV made no recommendation on whether NIV should be used or not in *de novo* hypoxemic respiratory failure because of the high failure rates and the conflicting evidence.

In contrast, HFNC has been gaining traction as a therapy for *de novo* hypoxemic respiratory failure. This is partly because HFNC is an effective oxygenator related to its ability to keep up with the high inspiratory flows of dyspneic, hypoxemic

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patients, reducing entrainment of room air that dilutes $F_{I_{O_2}}$ with standard oxygen systems. In addition, the flushing of nasal and oropharyngeal dead space means that the initial bolus of air at the start of inspiration is freshly oxygenated gas rather than oxygen-depleted gas that has just been exhaled (6).

The increasing use of HFNC to treat acute hypoxemic respiratory failure is also partly driven by accumulating evidence, although no guidelines have yet recommended this application. In the FLORALI study (7), a randomized controlled trial consisting of 310 patients with acute hypoxemic respiratory failure allocated to HFNC, NIV using a standard full-face mask, or standard oxygen, roughly 80% of enrollees had pneumonia/ARDS. Overall intubation rate (the primary outcome variable) did not differ between the groups, but in the subgroup with a $Pa_{O_2}/F_{I_{O_2}} \leq 200$, intubation rate was significantly lower in the HFNC group than in the other 2 groups. Moreover, the intensive care unit and 90-day mortality rates were significantly lower in the HFNC than in the standard oxygen and NIV groups (11%, 19%, and 25% for the intensive care unit and 12%, 23%, and 28% for 90-d mortality), respectively.

This and other studies have been influential in encouraging greater use of HFNC to treat hypoxemic respiratory failure. More recently, Patel and colleagues (8) have reported that NIV using a helmet device consisting of a clear plastic hood that fits over the head and affixes to the neck and shoulders drastically reduces intubation rate compared with a standard full-face mask (18% vs. 62%), as well as mortality (34% vs. 56%), raising the possibility that NIV administered via a better interface may still have a role in treating acute hypoxemic respiratory failure. Regardless of the noninvasive modality chosen, however, a major challenge in managing patients is to avoid delay of a needed intubation. In their study on use of NIV for postextubation respiratory insufficiency, Esteban and colleagues (9) found higher intensive care unit mortality in the NIV group, in which reintubations were performed an average of 10 hours later than in the control group. Similar findings were reported for HFNC in a retrospective cohort of 175 patients in whom late failure (after 48 h) was associated with worse outcomes than early failure. Thus, ways of predicting the likelihood of failure could be very helpful clinically, so that at-risk patients can be watched closer or even intubated earlier.

In this issue of the *Journal*, Roca and colleagues (pp. 1368–1376) (10) report results of their validation of the ROX index ([oxygen saturation/$F_{I_{O_2}}$]/respiratory rate) to predict outcomes of patients with hypoxemic respiratory failure resulting from pneumonia/ARDS treated with HFNC. Using a training cohort of 157 patients, they previously reported that a ROX value of >4.88 predicted success of HFNC (11). In the current study, the ROX index was validated in 191 patients enrolled at 5 centers in France and Spain who were sicker (more with shock and a trend toward a higher APACHE II score) and had a higher mortality (27.3%) than the training cohort (14.2%). Still, the ROX index score of >4.88 was as predictive of outcomes in the validation cohort as it was in the training cohort. The area under the curve at 12 hours, a measure of discrimination, was 0.752, which was comparable to the training cohort, and was higher than those of $Sp_{O_2}/F_{I_{O_2}}$ and Sp_{O_2} and $F_{I_{O_2}}$ singly at most points up to 24 hours. A second validation using patients from the FLORALI cohort (7) provided similar findings, although the areas under the curve were consistently lower than those in the first validation. It is worth noting that to fully validate a score, both discrimination (using area under the curve) and calibration (using observed outcomes) are important. Comparing predicted outcomes (based on the training cohort) versus observed outcomes at different levels of ROX in the validation cohort could have strengthened the validation.

The ROX score is likely to be useful clinically because it requires few data points and is simple to calculate at the bedside. It has a positive predictive value for success of HFNC of more than 80% between 12 and 20 hours postinitiation, when most of the intubations occur. For durations of use of less than 12 hours, when the ability to predict HFNC failure and the need for intubation would be important, the cutoff values of 2.85 at 2 hours, 3.47 at 6 hours, and 3.85 at 12 hours had specificities of 98–99% in the main validation cohort. Thus, clinicians could use the ROX score as a way to assess progress in patients receiving HFNC, making serial measurements, and incorporating it when considering decisions to escalate care. During the first 12 hours, scores below the cutoffs given here would prompt consideration of earlier intubation. Once the 12-hour point is reached, a score >4.88 increases clinician confidence that the patient will succeed. Caveats include the fact that the ROX score was developed in cohorts with hypoxemic respiratory failure resulting from pneumonia/ARDS and has not been validated in other populations. Also, no score can replace close bedside observation of critically ill patients with respiratory failure, but it can be helpful in more safely managing these patients, helping to avoid delayed intubations. Additional study would be necessary, however, to demonstrate that use of the ROX index can actually improve clinical outcomes, rather than just predict them. ■

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Respiratory Suffering in the ICU: Time for Our Next Great Cause

Dyspnea, or breathlessness, ranks among the worst suffering that a human being can experience. Although it is similar to pain in many ways, dyspnea differs from pain in its terrifying dimension. Having trouble taking a breath in, experiencing an unquenchable thirst for air, or feeling one's chest constricted immediately summons an existential fear, the fear of dying. This makes the relief of dyspnea a primary concern, anchored not only to clinical obligation but also to universal ethical and moral considerations (1, 2).

Relief of dyspnea implies its recognition. When the dyspneic patient can talk, the patient's own report of having difficulty breathing is emphasized in the current operational definition of dyspnea (3). It is straightforward to elicit, if one takes the trouble to do so (4). When verbal communication is impaired for whatever reason, dyspnea-related clinical manifestations can be missed. Dyspnea then remains occult (5), compounding the perception of an existential threat with a sensation of powerlessness. This leads to panic and is a clear recipe for post-traumatic stress disorder (1). Yet there are many nonverbal dyspnea-related signs (neurovegetative, behavioral, and emotional) that allow the identification of breathlessness in noncommunicative patients (6–9).

In this issue of the *Journal*, Gentzler and colleagues (pp. 1377–1384) confirm that dyspnea is as frequent a problem for patients in the ICU as pain (10). In their study, moderate to severe dyspnea was reported by 47% of patients, and 41% of patients reported pain. One of their most striking findings is that the performance of nurses in identifying dyspnea was relatively poor; personal caregivers performed much better. Personal caregivers' ratings of dyspnea agreed well with the patients' own ratings, but this was far from being the case for the nurses' ratings. The poor aptitude of nurses, physiotherapists, and physicians in identifying dyspnea in their patients has been described before (11–13), but this is the first time that a comparison has been conducted with the corresponding aptitude of personal caregivers, who, notably, never failed to detect dyspnea.

Improving the performance of ICU personnel in identifying dyspnea and evaluating its severity therefore seems necessary. Implementing systematic dyspnea assessments in routine clinical care (as for pain) could be useful (14), and such routine assessments seem readily acceptable to nurses (15). Generalizing the use of observational scales (and particularly their simplified ICU versions [7–9]) could also be useful (16). Specific studies should be designed to determine the potential benefits of such approaches. Electromyographic and electroencephalographic techniques offer the prospect of improving this process by providing surrogate biomarkers of dyspnea (17–19).

But identifying dyspnea is not enough. It is necessary to do something about it. Perhaps the most important finding of the study by Gentzler and colleagues is that nurse detection of moderate-to-severe dyspnea was not associated with any therapeutic action, such as administering bronchodilators or opioids, adjusting ventilator settings, or changing the respiratory device altogether. This stood in contrast to pain, whose detection was significantly associated with opioid treatment. This finding is not completely surprising. A recent survey showed that clinicians confronted with theoretical cases of chronic pain or "chronic breathlessness" (20), or "persistent breathlessness" (21), acted far more on the pain than on the dyspnea (22). The term "invisibility of dyspnea" was coined to describe the lack of response of caregivers to dyspnea, or even their avoidance of it (23, 24). There are several possible reasons for this surprising observation. First, dyspnea, in contrast to pain, is not a universal experience. The shortness of breath that healthy people experience during exertion cannot be compared with pathological breathlessness (25). It is unthreatening—it can even be satisfactory—and it can be controlled by reducing the intensity of exertion. It is thus likely that it is more difficult for a caregiver to identify with the suffering of dyspna than with the suffering of pain. Second, and also in contrast to pain, there are no firmly established guidelines to manage dyspnea in ICU patients. This can make caregivers feel helpless and, as a reaction, favor avoidance. The nurses in Gentzler and colleagues study emphasized that dyspnea presented a greater challenge to symptom management than pain, yet dyspnea in mechanically ventilated patients

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