approach probably accounts for individual lung recruitability better than an arbitrary oxygenation scale. The Express study demonstrated that such an approach could be incorporated in the protocol and disseminated across multiple centers. It also is reassuring that a higher level of PEEP with plateau pressure limitation (in the ranges used in these 2 studies) does not induce harm. In contrast, the findings of these 2 studies do not support a strategy of using a lower level of PEEP. A lower level of PEEP produces a greater number of patients with severe hypoxemia at high risk of death and for whom clinicians feel pressed to embark on rescue therapy. The Express study suggests lower PEEP is associated with fewer ventilator-free and organ failure–free days.

Thus, strategies with higher levels of PEEP, as tested in these 2 clinical trials, appear safe and probably beneficial, especially in patients with ALL and ARDS who are the most sick, whereas strategies with lower levels of PEEP may worsen outcomes.

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Testing Protocols in the Intensive Care Unit

Complex Trials of Complex Interventions for Complex Patients

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In this issue of JAMA, Meade and colleagues1 and Mercat and colleagues2 report the results of 2 large international trials of alternative strategies for setting positive end-expiratory pressure (PEEP) in ventilated patients with acute lung injury or acute respiratory distress syndrome. Both trials asked whether higher PEEP would reduce mortality, and both concluded it did not. Many readers not familiar with intensive care might reasonably wonder why such a seemingly innocuous intervention would deserve such attention, but the story behind PEEP is a long one, and these latest, largest trials do not provide a conclusion. They do, however, serve to demonstrate that answering this question is far from simple.

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See also pp 637, 646 and 691.
Mechanical ventilation is lifesaving for patients with acute lung injury or acute respiratory distress syndrome, but the ventilator can injure the lung, causing a condition known as ventilator-induced lung injury. The most successful way to minimize ventilator-induced lung injury was demonstrated by the NHLBI Acute Respiratory Distress Syndrome Network: a protocol to lower tidal volumes, compared with a protocol that required higher tidal volumes, improved survival. This important result was both praised and criticized: proponents argued that low tidal volume protocols should be implemented broadly, but others cautioned that simply reducing tidal volume to a specific level (6 mL/kg of predicted body weight) failed to fully consider the complex mechanics of the injured lung. For example, the benefits of avoiding overdistention with lower tidal volumes may be negated in some patients by worsened atelectasis, collapse, or repetitive alveolar open-close shearing with each breath.

Experimental data favor the combination of lower tidal volumes with higher PEEP to achieve an optimal balance of maximal recruited lung with minimal overdistention. However, such titration at the bedside is complex and was previously considered the domain of the expert clinician. The 2 trials reported in this issue tested sophisticated protocols that were designed to set PEEP in a reproducible fashion yet titrate it to individual requirements. The Lung Open Ventilation Study took the simplest approach, titrating PEEP yet titrating it to individual requirements. The Lung Open Ventilation and Express studies chose to standardize the care of these critically ill patients, especially in a multicenter environment, is a huge task that may distort usual practice and engender considerable resistance. An alternative is collecting the information necessary to determine whether use of cointerventions was dramatically different across treatment groups. Although more feasible, this effort still represents a considerable logistic and financial burden, does not prevent confounding, and provides only circumstantial evidence as to whether confounding occurred. For example, in both trials, patients who received higher PEEP were less likely to require rescue therapy. Possible explanations are that higher PEEP protected lungs and facilitated recovery; that higher PEEP simply made the patient appear less sick by improving oxygenation without fundamentally changing the risk of death; or that clinicians had greater trust in higher PEEP and therefore felt less need to take additional measures.

Second, defining the control intervention is of crucial importance. The ideal approach is to compare a new intervention with the best current standard of care. However, when the intervention is a complex set of instructions, the alternative could be myriad expert clinician behaviors that are difficult to quantify and reproduce. Both the Lung Open Ventilation and Express studies chose to standardize the care in the control intervention by promoting the use of low tidal volume protocols similar to that tested by the NHLBI Acute Respiratory Distress Syndrome Network. The advantage of this approach is that the intervention in the control group is more explicit, thereby promoting greater confidence in the study’s generalizability to other settings where protocols with low tidal volumes are the current standard of care.

First, these trials are unblinded. Blinding a complex set of clinician instructions is obviously not practical, but failing to do so exposes the study results to potentially important biases. In particular, clinicians may alter their behavior with regard to other aspects of care based on knowledge of treatment assignment. To reduce the risk of such bias, all aspects of care that affect study outcomes could be described in the protocol. In the Express trial, for example, the investigators disseminated standard instructions for managing hemodynamic changes secondary to ventilator adjustments. However, writing a protocol to include all potential cointerventions used in the care of these critically ill patients, especially in a multicenter environment, is a huge task that may distort usual practice and engender considerable resistance. An alternative is collecting the information necessary to determine whether use of cointerventions was dramatically different across treatment groups. Although more feasible, this effort still represents a considerable logistic and financial burden, does not prevent confounding, and...
more formal evaluation of compliance with the protocols, and prespecified secondary analyses that accounted for intersite variation in compliance, may have provided insight into the failure to detect a difference in mortality. Information on steps taken to ensure compliance would also be helpful should there be attempts to disseminate higher PEEP strategies to clinical practice.

In summary, despite the relatively straightforward physiologic basis for the individualized titration of the “best” PEEP, generation of robust clinical evidence in its favor is bedeviled by a number of complicated study design choices and implications. Issues largely solved for placebo-controlled drug trials resurface when testing these complex interventions. Nevertheless, both the Lung Open Ventilation Study and the Express Study demonstrated that it was possible to convert the physiologic principles on which experts base their care into a set of reproducible instructions and then test these instructions in a broad multicenter environment. Although neither study demonstrated a significant improvement in mortality, their findings appear to have implications for future practice. Finally, these studies made important steps toward increasingly rigorous assessment of increasingly sophisticated protocols for the best care of critically ill patients.

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Academic Medical Centers and Financial Conflicts of Interest

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ver the past decade, concern about the consequences of financial conflict of interest has escalated dramatically. Although the principle that the integrity of decision making should not be undermined by self-interest may seem self-evident, not until the 1960s was this concept applied to government office holders and attorneys, and then sporadically in the 1980s and 1990s to physicians and clinical researchers. Indeed, it is only now that academic medical centers (AMCs) and professional medical societies are more systematically addressing many of the critical issues involved in institutional conflicts of interest (ICOI). Many leaders and administrators at AMCs are asking how scientific objectivity can be maintained considering the potentially compromising relationships that can ensue from gifts, grants, royalties, equity holdings, and business ownership—not only to individual investigators and clinicians, but also to academic institutions.

As is often the case, it takes a scandal to set off alarms and medical practice has recently generated many alarms and concerns. The easiest cases to draw attention are individual conflicts of interest, as evidenced by extensive media coverage about clinicians who use devices manufactured by companies they own, clinicians who prescribe and overprescribe drugs manufactured by companies that pay them hefty consulting and speaker fees, and researchers who have a financial stake in the outcome of the drug or device they are testing.

Exposure does not necessarily prompt antidotes but notable progress is being made in managing and reducing individual conflicts of interest. Although some can still claim that “modest gifts are harmless,” or that “research integrity cannot be undermined by the lure of profits,” federal regulations and AMC procedures are becoming far more rigorous. The guidelines on pharmaceutical company–clinician relationships issued by the American Medical Association and also by the Pharmaceutical Research and Manufacturers of America have been superseded by stricter, if not entirely satisfactory, guidance from the Office of Inspector General, US Department of Health and Human Services. More