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It is possible that a three-dose series is daunting to parents of teens and their clinicians, whether because of the cost (even if borne by private insurance or the VFC program) or the difficulty of making three office visits during a stage when school and extracurricular activities can be all-consuming. Expanding in-network insurance coverage to pharmacies could present a convenient option for the completion of multi-dose series during the teenage years, but immunization data for these encounters should be made accessible to primary care physicians through immunization information systems. Regulatory authorities in several countries have approved two-dose series for young adolescents for both the quadrivalent and bivalent HPV vaccine based on the noninferior immunogenicity of two doses administered 6 months apart.⁸ The ACIP has reviewed available data for two-dose schedules and will review forthcoming data on the immunogenicity of alternative schedules for the 9-valent vaccine.

Even with the availability of another HPV vaccine targeting additional cancer-causing virus types, vaccination of a much higher proportion of preteens is needed. Otherwise, decades from now oncologists will still be talking about HPV-associated cancers with thousands of new patients every year. Instead, I hope that in a few

decades we will be able to tell a generation of adults who never had HPV-associated cancers or precancers that when they were teenagers, we had them covered.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Centers for Disease Control and Prevention, Atlanta.

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Driving Pressure and Respiratory Mechanics in ARDS

Stephen H. Loring, M.D., and Atul Malhotra, M.D.

In this issue of the *Journal*, Amato et al.¹ use data from previously published trials to determine whether it is possible to predict outcomes in patients with the acute respiratory distress syndrome (ARDS) on the basis of the settings of their mechanical ventilators or parameters derived from monitoring the mechanics of the ventilation achieved. Previous articles published in the *Journal* had shown that a lung-protective strategy — that is, limiting the tidal volume (V_T) and plateau pressure while providing relatively high positive end-expiratory pressure (PEEP), can improve survival in ARDS,^{2,3} thus demonstrating the importance of respiratory mechanics in determining outcomes in patients.⁴ Lung-protective ventilation strategies maintain alveolar aeration, prevent overexpansion of the lung, and limit

driving pressure (ΔP , which can be calculated as ventilator-measured plateau pressure minus applied PEEP) and thereby are thought to reduce ventilator-induced lung injury.

Amato et al. focus on ΔP as a predictor of outcome in ARDS. Because ΔP is the tidal increase in static transrespiratory pressure, it is proportional to V_T with respiratory-system elastance (the inverse of compliance) being the constant of proportionality; elastance reflects the severity and extent of lung injury. Thus, ΔP is determined by variables known to predict or affect mortality in ARDS. The authors conducted a statistical mediation analysis of the aforementioned data, in which variations of V_T , PEEP, ΔP , and respiratory-system compliance were assessed to determine which of the operator-set or measured variables was most

closely linked to outcomes. They concluded that ΔP was the variable most closely related to survival.

Several concepts are important in the consideration of these findings. First, transpulmonary pressure (the pressure difference from airway opening to pleural space) is the relevant distending pressure for the lung.⁵ This concept is often overlooked when practitioners focus on the plateau pressure without considering the effect of the chest wall in determining lung expansion and stress.^{6,7} High transpulmonary pressures can cause lung injury resembling ARDS or gross barotrauma in the form of pneumothorax. Indeed, abundant data have shown that low V_T , and consequently lower plateau and transpulmonary pressures, improve survival.³ Importantly, ΔP limitation may not be helpful for patients who are actively breathing and who have pleural-pressure decreases during inspiration as a result of their own efforts to breathe in that result in high transpulmonary pressures. Second, atelectrauma,⁸ caused by the repetitive collapse and reexpansion of lung units, has been shown to be damaging. Lung collapse can result from surfactant dysfunction, in which case surfactant fails to have its physiologic effect and the surface tension of alveolar-lining fluid becomes high, promoting alveolar collapse. Collapse can also occur when elevated pleural pressures — for example, caused by pleural effusions, obesity, or ascites — effectively compress the lung externally.⁶ Applying adequate PEEP can help to prevent collapse of the lung at end exhalation and thus prevent atelectrauma.^{4,8,9}

The ability of ΔP to predict outcome is attributable to the fact that the variables that define it are themselves highly predictive of survival. As the authors emphasize, previous studies were not designed to assess ΔP as an independent variable, and thus the findings reported by Amato et al. should be considered hypothesis-generating rather than definitive. The authors argue for the “baby lung” concept, in which some portion of the lung in patients with ARDS is collapsed or flooded and thus does not participate in gas exchange, leaving the rest of the lung (i.e., the “baby lung”) to effect gas exchange.¹⁰ If this is the case, limiting ΔP may be a way to scale the delivered breath to the size of the lung that is available to participate in gas exchange, rather than scaling to body size, which may be less biologically relevant. Although the concept of limiting ΔP is appealing, the question of whether the

manipulation of ΔP rather than V_T is beneficial remains. Designing prospective, randomized trials to assess the independent role of high versus low ΔP in clinical outcomes will be complicated and will require consideration of the effect that limiting ΔP has on V_T and subsequent minute ventilation, as indicated by levels of carbon dioxide in arterial blood, as well as the fact that a given ΔP would have very different effects depending on the PEEP level chosen (e.g., a PEEP of 5 cm of water vs. 15 cm of water).

Is a strategy in which ventilators are set to limit ΔP superior to our current approach? We strongly urge caution in accepting the idea that limiting ΔP is what we should do at the bedside now. Instead, the meta-analytic findings reported by Amato et al. form the basis for a robust debate regarding how to design a controlled trial to be sure the idea of limiting ΔP is correct. Although the design of such a trial will not be easy, the problem is important. In the words of Piet Hein, “Problems worthy of attack prove their worth by hitting back.”

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