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Evidence and Our Daily Risk Trade-offs in the Care of Critically Ill Patients

When faced with critically ill patients, clinicians frequently face treatment decisions despite limited evidence for guidance. They must weigh the risks and benefits of a potential therapy and any associated evidence against the risk of death and morbidity faced by the patient. Optimistic and early observational studies are sometimes the best quality of evidence available and compel clinicians to adopt therapies with modest evidence in the setting of severely ill patients. But this embrace of early observational studies under stress is in striking conflict with our poor track record of routine adoption of clinical strategies with strong evidence or our unwillingness to deadopt therapies when strong evidence refutes our current practice.

In this issue of the *Journal*, Vail and colleagues (pp. 1531–1539) explore this tension between evidence, action, and adoption in the context of hydrocortisone, ascorbic acid, and thiamine (HAT) therapy for septic shock (1). The authors sought to examine patterns of HAT use and associated outcomes among U.S. adults with septic shock before and after the December 2016 online publication of a widely publicized single-center HAT therapy study by Marik and colleagues (2). To this end, they conducted a retrospective cohort study using data from between October 1, 2015, and June 30, 2018, from the Premier Healthcare Database. The authors examined temporal trends in HAT administration across quarter-years of hospital discharge in the prepublication and postpublication periods. They subsequently examined patient- and hospital-level factors associated with HAT administration and modeled the association between HAT administration and mortality in the postpublication period.

Vail and colleagues demonstrate that HAT therapy use increased markedly in the period after the publication of Marik and colleagues' paper (adjusted odds ratio [OR], 26.81; 95% confidence interval [CI], 14.52–49.53) and continued quarterly thereafter (per-quarter adjusted OR, 1.49; 95% CI, 1.19–1.86). In addition to noting a substantial increase in HAT use over time, the hospital of admission was strongly associated with the receipt of HAT (adjusted median OR, 12.06; 95% CI, 9.12–16.51). As anticipated, sicker patients were also more likely to receive HAT. In multivariable and propensity-matched analyses adjusting for patient- and hospital-level confounders, the odds of hospital mortality were higher among patients who received HAT therapy (multivariable model: adjusted OR, 1.17; 95% CI, 1.02–1.33). Vail and colleagues' findings tell us that although randomized controlled trials were underway to evaluate Marik and colleagues' observational findings, many clinicians were willing to adopt the practice before those results returned.

Clinicians are historically slow both to adopt strongly evidence-based therapies and, when adopted, to deadopt if evidence refutes our habits (3). For example, we know that placing patients in the prone position is an inexpensive therapy with strong evidence supporting mortality benefit for patients with acute respiratory distress syndrome (4). However, in a survey of ICUs in Massachusetts, only 44% of the ICUs reported routinely using prone positioning when indicated (the equivalent of approximately 60% of all ICU beds in the state) (5). Even more striking, we have known for 20 years that lung protective ventilation saves lives, but over one-third of patients in the LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) study received V_Ts over 8 ml/kg ideal body weight (4, 6). Of course, the challenge of evidence adoption is not unique to critical care. This delay in adoption has been highlighted in many areas of medicine; for example, the limited rate at which U.S. outpatients receive evidence-based, recommended preventive care is a disappointing 55% (7).

Why does healthcare practice have such difficulty pairing evidence with adoption? Many explanations seem to point to physicians, including our training, which emphasizes experiential learning and apprenticeship, and our shortages

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of time. Qualitative investigations into limited adoption of routine, evidence-defined practices have found that physicians may lack the statistical background to meaningfully interpret results from the literature, are challenged by limited time, and are influenced by their training and their colleagues more than routinely published evidence (8). Rubenfeld and colleagues identified factors including *1*) acute respiratory distress syndrome recognition and *2*) perceived patient contraindications to lung protective ventilation as some of the major drivers of non–evidence-based ventilation strategies (9).

So, what made Marik and colleagues' study so appealing as to explain the marked change in administering this therapy after only one single-center study, without waiting for larger ongoing randomized controlled trials? One possible explanation is the ease of use. Rather than requiring the management of complex ventilator settings or gathering a multidisciplinary team to transfer a patient to their stomach, HAT is an intervention that only required the administration of available medications. Physicians are more likely to choose a less effort-intensive task over a more difficult one, particularly in times of stress (10).

Alternatively, physicians' embrace of Marik and colleagues' findings may reflect the substantial variation in physician behavior when faced with an uncertain "risk trade-off." The concept of a risk trade-off comes from the human factors literature of other high-risk professions and reflects the burden placed on an individual to weigh different risks in the setting of uncertainty, resource constraints, and a varying context to arrive at what is perceived to be the safest choice. One investigation into risk trade-offs among ICU physicians found that variation in perceptions of risk led to substantial variation in care choices and, by extension, outcomes for patients (11). In the case of HAT therapy, when one side of the risk equation represents perceived low-risk medications, the threshold to use therapies with limited evidence may decrease. Perhaps Vail and colleagues' higher mortality among patients in whom HAT therapy was used indicates that physicians caring for these patients felt compelled to act because of the high risk of death among patients in their care.

These challenges are particularly relevant to our current context caring for acutely ill patients with coronavirus disease (COVID-19) and the willingness among clinicians to use untested therapies among severely ill patients. The change in practice that Vail and colleagues documented after a single observational trial is now being repeated over and over again after each observational study looking for new therapies for COVID-19. The human factors literature tells us that the daily risk trade-offs experienced by clinicians while caring for acutely ill patients with COVID-19 will lead to a series of highly variable behaviors, enthusiasm for untested therapies, and patient outcomes. Both timely and robust clinical evidence, coupled with implementation science to aid in bringing evidence into practice, have never been more essential to meet the challenges of critical illness—taking appropriate therapies to the bedside, ensuring effective delivery of evolving treatment paradigms, and deadopting therapies if high-quality evidence to the contrary arrives. ■

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