Michael A. Matthay, M.D.
Department of Medicine
and
Department of Anesthesia
University of California, San Francisco
San Francisco, California

Aleksandra Leligdowicz, M.D., Ph.D.
Department of Medicine
and
Department of Anesthesia
University of California, San Francisco
San Francisco, California
and
Interdepartmental Division of Critical Care Medicine
University of Toronto
Toronto, Canada

Kathleen D. Liu, M.D., Ph.D., M.A.S.*
Department of Medicine
and
Department of Anesthesia
University of California, San Francisco
San Francisco, California

ORCID IDs: 0000-0003-3039-8155 (M.A.M.); 0000-0001-6055-4644 (A.L.).

*K.D.L. is Associate Editor of *AJRCCM*. Her participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

References

1. CDC COVID Data Tracker. [updated 2020 Oct 20; accessed 2020 Sep 23]. Available from: https://covid.cdc.gov/covid-data-tracker.
2. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, *et al*. Incidence and outcomes of acute lung injury. *N Engl J Med* 2005; 353:1685–1693.
3. Hue S, Beldi-Ferchiou A, Bendib I, Surenaud M, Fourati S, Frapard T, *et al*. Uncontrolled innate and impaired adaptive immune responses in patients with COVID-19 acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020;202:1509–1519.
4. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, *et al*. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* 2020;369:718–724.
5. Wang BX, Fish EN. Global virus outbreaks: interferons as 1st responders. *Semin Immunol* 2019;43:101300.
6. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol* 2020;38:1–9.
7. Kuri-Cervantes L, Pampena MB, Meng W, Rosenfeld AM, Ittner CAG, Weisman AR, *et al*. Comprehensive mapping of immune perturbations associated with severe COVID-19. *Sci Immunol* 2020;5: eabd7114.
8. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, *et al*. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in covid-19. *N Engl J Med* 2020;383:120–128.
9. Grasselli G, Tonetti T, Protti A, Langer T, Girardis M, Bellani G, *et al*.; collaborators. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. *Lancet Respir Med* [online ahead of print] 27 Aug 2020; DOI: 10.1016/S2213-2600(20)30370-2.
10. Radermecker C, Detrembleur N, Guiot J, Cavalier E, Henket M, d'Emal C, *et al*. Neutrophil extracellular traps infiltrate the lung airway, interstitial, and vascular compartments in severe COVID-19. *J Exp Med* 2020;217:e20201012.
11. Ji HL, Zhao R, Matalon S, Matthay MA. Elevated Plasmin(ogen) as a common risk factor for COVID-19 susceptibility. *Physiol Rev* 2020; 100:1065–1075.
12. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, *et al*.; RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with covid-19 - preliminary report. *N Engl J Med* [online ahead of print] 17 Jul 2020; DOI: 10.1056/NEJMoa2021436.
13. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. *Nat Rev Immunol* 2017;17:233–247.
14. Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, *et al*. Acute respiratory distress syndrome. *Nat Rev Dis Primers* 2019; 5:18.
15. Bao L, Deng W, Huang B, Gao H, Liu J, Ren L, *et al*. The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice. *Nature* 2020;583:830–833.
16. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, *et al*.; ACTT-1 Study Group Members. Remdesivir for the treatment of covid-19 - preliminary report. *N Engl J Med* [online ahead of print] 22 May 2020; DOI: 10.1056/NEJMoa2007764.

Noninvasive Ventilation for Acute Asthma: The Neglected Sibling

Invasive mechanical ventilation (IMV) is lifesaving for patients suffering from acute respiratory failure but is not without drawbacks. The introduction of noninvasive ventilation (NIV) revolutionized the management of acutely ill patients with respiratory failure and, when implemented in the appropriate patient population, offers a lifesaving alternative to IMV. Like any medical intervention, however, improper use or patient selection can result in significant harm. Since its introduction, NIV has become standard of care for multiple indications supported by robust randomized controlled trials, although evidence for other indications remains less certain (1). When used in respiratory failure due to acute cardiogenic pulmonary edema, NIV can reduce both need for endotracheal intubation and mortality (2–4). For patients with respiratory failure due to an exacerbation of chronic obstructive pulmonary disease (COPD), NIV offloads fatiguing respiratory muscles resulting from bronchial obstruction and hyperinflation. Thus, a well-established evidence base has demonstrated its efficacy in preventing intubation and reducing mortality in these patients (5, 6).

Although asthma shares a similar pathophysiology to COPD, evidence supporting the use of NIV for acute asthma has

S.D.P. is supported by NIH/NHLBI T32 HL 7605-35, and B.K.P. is supported by NIH/NHLBI K23 HL 148387.

Originally Published in Press as DOI: 10.1164/rccm.202007-2876ED on August 5, 2020

remained limited. The few randomized controlled clinical trials have shown some improvement in physiologic markers but were underpowered for more meaningful clinical outcomes (7–9). Although a Cochrane systematic review of five small randomized controlled clinical trials evaluating the effect of NIV in acute asthma showed an improvement in pulmonary function, respiratory rate, and hospital admissions, the aggregate analysis remained underpowered for in-hospital mortality and endotracheal intubation (10). Consequently, the 2017 combined European Respiratory Society/American Thoracic Society clinical practice guidelines on NIV for acute respiratory failure were unable to provide a recommendation for or against the use of NIV in acute asthma (11).

Given the uncertainty of available evidence and lack of consensus guidelines, the use of NIV in acute asthma has remained controversial. Despite this, it has been widely adopted with increased use over the past two decades (12). What might explain such pervasive use of an intervention without proven clinical benefit in this patient population? Various theories have been put forth including an assumed benefit given the pathophysiologic similarities between asthma and COPD coupled with growing comfort and familiarity with NIV (13). Regardless of the reason, this increased usage has facilitated a growing literature of large-scale observational studies assessing the clinical outcomes of patients with acute asthma managed with NIV, which has largely suggested an association with improved outcomes (12, 14).

In this issue of the *Journal*, Althoff and colleagues (pp. 1520–1530) add to this growing body of observational evidence with a large retrospective cohort study of adult patients with acute asthma admitted to the ICU examining the association between NIV use, need for endotracheal intubation, and in-hospital mortality and exploring their temporal trends (15). The authors used three unique multivariate models to assess this association and found that NIV was associated with a reduction in endotracheal intubation (adjusted generalized estimating equation odds ratio, 0.36; 95% confidence interval, 0.32–0.40) and in-hospital mortality (odds ratio, 0.48; 95% confidence interval, 0.40–0.58) across all models. The study also found patients failing NIV were more likely to have acute comorbidities such as pneumonia, sepsis, and acute renal failure. Interestingly, although those who failed NIV had a higher mortality than the overall population, their mortality was still lower than that of patients receiving IMV alone.

The study by Althoff and colleagues has many strengths and includes the largest cohort of adult patients who received NIV for acute asthma to date. The authors conducted a robust analysis using multiple statistical models, all of which support their main findings. These findings, although novel, align with the currently available evidence base. Despite the aforementioned strengths, the study is not without its limitations, first and foremost being its retrospective nature precluding randomization. Although the authors used propensity score matching to minimize selection bias, the variables used to match controls on acuity of illness and severity of asthma (including prior IMV) were limited. Furthermore, temporality of comorbid conditions could not be assessed owing to reliance on diagnosis codes, and conditions associated with NIV failure (pneumonia, acute renal failure, and severe sepsis) may have occurred as a complication of IMV as opposed to being a risk factor for NIV failure. Lastly, and perhaps most importantly, despite a marked increase in the proportion of patients with acute asthma managed with NIV over the study years, there was no significant change in the proportion of patients who received IMV or died. This finding is similar to other published data showing increased NIV use without a decrease in IMV in acute asthma (12). Taken together, this observation suggests that NIV is likely being used in lower-risk patients with acute asthma who may not require ventilatory support of any kind. To explore this, the authors performed a subgroup analysis of patients with a primary diagnosis of respiratory failure, thought to be a more critically ill group, and found that increased NIV use in this subgroup was accompanied by a decrease in IMV. However, more patients may have received a primary diagnosis of respiratory failure as a result of receiving NIV itself as opposed to objective measures of severity of respiratory illness, confounding this finding.

What comes next in the story of NIV for acute asthma? In light of widespread adoption and mounting observational evidence, it is unlikely that randomized controlled trials powered to detect an improvement in meaningful clinical outcomes are on the horizon. Thus, acute asthma may remain a neglected sibling in the robust clinical trial evidence for the efficacy of NIV. However, based on the in-depth and large-scale data provided by Althoff and colleagues, NIV appears to be a safe and well-tolerated intervention, possibly even in those who ultimately require IMV. Whether NIV reduces the need for endotracheal intubation or mortality, however, remains far from certain. Future studies may aim to determine whether NIV is a viable and effective alternative to IMV for patients presenting with severe acute asthma requiring ventilatory support, as these patients stand to suffer the most harm from a gap in the evidence base. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Steven D. Pearson, M.D.
Bhakti K. Patel, M.D.
Section of Pulmonary & Critical Care
University of Chicago
Chicago, Illinois

ORCID IDs: 0000-0003-4384-5874 (S.D.P.); 0000-0002-6517-2175 (B.K.P.).

References

1. Mehta S, Hill NS. Noninvasive ventilation. *Am J Respir Crit Care Med* 2001;163:540–577.
2. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J; 3CPO Trialists. Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med* 2008;359:142–151.
3. Masip J, Betbesé AJ, Páez J, Vecilla F, Cañizares R, Padró J, *et al*. Non-invasive pressure support ventilation versus conventional oxygen therapy in acute cardiogenic pulmonary oedema: a randomised trial. *Lancet* 2000;356:2126–2132.
4. Vital FMR, Ladeira MT, Atallah AN. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. *Cochrane Database Syst Rev* 2013; (5):CD005351.
5. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, *et al*. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995;333:817–822.
6. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2017;7:CD004104.
7. Brandão DC, Lima VM, Filho VG, Silva TS, Campos TF, Dean E, *et al*. Reversal of bronchial obstruction with bi-level positive airway pressure and nebulization in patients with acute asthma. *J Asthma* 2009;46:356–361.

8. Gupta D, Nath A, Agarwal R, Behera D. A prospective randomized controlled trial on the efficacy of noninvasive ventilation in severe acute asthma. *Respir Care* 2010;55:536–543.
9. Soroksky A, Stav D, Shpirer I. A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. *Chest* 2003;123:1018–1025.
10. Lim WJ, Mohammed Akram R, Carson KV, Mysore S, Labiszewski NA, Wedzicha JA, *et al*. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. *Cochrane Database Syst Rev* 2012;12: CD004360.
11. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, *et al*. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J* 2017;50: 1602426.
12. Stefan MS, Nathanson BH, Priya A, Pekow PS, Lagu T, Steingrub JS, *et al*. Hospitals' patterns of use of noninvasive ventilation in patients with asthma exacerbation. *Chest* 2016;149:729–736.
13. Scala R. Noninvasive ventilation for acute asthma. "Spill-over" or "lighted windows"? *Ann Am Thorac Soc* 2016;13:1005–1007.
14. Stefan MS, Nathanson BH, Lagu T, Priya A, Pekow PS, Steingrub JS, *et al*. Outcomes of noninvasive and invasive ventilation in patients hospitalized with asthma exacerbation. *Ann Am Thorac Soc* 2016;13: 1096–1104.
15. Althoff MD, Holguin F, Yang F, Grunwald GK, Moss M, Vandivier RW, *et al*. Noninvasive ventilation use in critically ill patients with acute asthma exacerbations. *Am J Respir Crit Care Med* 2020;202:1520–1530.

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

Originally Published in Press as DOI: 10.1164/rccm.202007-2898ED on August 10, 2020