References

1 World Health Organization. WHO coronavirus disease (COVID-19) dashboard. 2020 [accessed 2021 Feb 18]. Available from: https://covid19.who.int/.
2 Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020;324:603–605.
3 Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, *et al.* 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021;397:220–232.
4 Logue JK, Franko NM, McCulloch DJ, McDonald D, Magedson A, Wolf CR, *et al.* Sequelae in adults at 6 Months after COVID-19 infection. *JAMA Netw Open* 2021;4:e210830.
5 Xiong Q, Xu M, Li J, Liu Y, Zhang J, Xu Y, *et al.* Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. *Clin Microbiol Infect* 2021;27:89–95.
6 Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, *et al.* Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine* 2020;25:100463.
7 Huang Y, Tan C, Wu J, Chen M, Wang Z, Luo L, *et al.* Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respir Res* 2020;21:163.
8 Venturelli S, Benatti SV, Casati M, Binda F, Zuglian G, Imeri G, *et al.* Surviving COVID-19 in Bergamo province: a post-acute outpatient re-evaluation. *Epidemiol Infect* 2021;149:e32.
9 Tenforde MW, Kim SS, Lindsell CJ, Billig Rose E, Shapiro NI, Files DC, *et al.*; IVY Network Investigators; CDC COVID-19 Response Team; IVY Network Investigators. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network—United States, March–June 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:993–998.
10 Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, *et al.* Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect* 2020;81:e4–e6.
11 National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19. 2020 [accessed 2021 Feb 15]. Available from: https://www.nice.org.uk/guidance/ng188.
12 Maurizi CP. Postencephalitic Parkinson's disease, amyotrophic lateral sclerosis on Guam and influenza revisited: focusing on neurofibrillary tangles and the trail of tau. *Med Hypotheses* 2002;58:198–202.
13 Townsend L, Dowds J, O'Brien K, Sheill G, Dyer AH, O'Kelly B, *et al.* Persistent poor health after COVID-19 is not associated with respiratory complications or initial disease severity. *Ann Am Thorac Soc* 2021;18:997–1003.
14 Centers for Disease Control and Prevention. Risk for COVID-19 infection, hospitalization, and death by race/ethnicity. 2021 [accessed 2021 Feb 18]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html.
15 Sze S, Pan D, Nevill CR, Gray LJ, Martin CA, Nazareth J, *et al.* Ethnicity and clinical outcomes in COVID-19: a systematic review and meta-analysis. *EClinicalMedicine* 2020;29:100630.
16 Lam MH, Wing YK, Yu MW, Leung CM, Ma RC, Kong AP, *et al.* Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up. *Arch Intern Med* 2009;169:2142–2147.

Acute Respiratory Distress Syndrome following Hematopoietic Stem Cell Transplantation: One More Piece in the Puzzle

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Critical illness across patients with cancer no longer means end of life. Over time, oncologic critical care outcomes have witnessed one of the greatest reductions in mortality when compared with other vulnerable populations (1). These improvements are attributable to advancements in cancer care, infectious disease, and critical care practices (2). Critical care mortality trajectories within oncology continue to improve with time as both fields venture further into precision medicine and bio-phenotyping (3–5).

Hematopoietic cell transplantation (HCT) is a potentially curative therapy for patients with malignant and nonmalignant hematologic disorders. However, patients undergoing HCT have remained especially vulnerable in the face of critical illness, particularly acute respiratory distress syndrome (ARDS) (6, 7). Indeed, historic guidelines had advised against intensive care unit admission for this population based on early data highlighting excessive mortality (8, 9). The reasons for the higher mortality are likely multifold and in part owing to mechanistic differences in ARDS compared with the general population. Although neutrophil response plays a central role in the development of ARDS, Braude and colleagues first described how neutropenic HCT recipients could develop

ARDS (10), highlighting diverse pathophysiology underlying ARDS. ARDs in HCT recipients occurs frequently outside of the neutropenic period with unique causes that occur at distinct time points posttransplant. Understanding these mechanistic differences within HCT as time posttransplant evolves and between HCT and non-HCT recipients is critical to ultimately improve outcomes.

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As critical care and oncologic practices evolved over time, the HCT population similarly experienced improvements in mortality (5, 11). A greater understanding of ventilator-associated lung injury, the role of noninvasive oxygen strategies, infection identification, and targeted antimicrobial therapies were likely major factors impacting outcomes in this population. Unfortunately, however, this cohort has not experienced the same quantum of improvement compared with other oncology subtypes (3). In fact, recent data show a plateauing of critical care–associated mortality compared with other oncology subgroups in which mortality continues to improve (3).

In the face of this deceleration, as intensivists, we are left asking ourselves: Can we move the needle to further ameliorate outcomes? Is the mortality plateau because of *1*) our limited understanding of the pathophysiology of HCT–ARDS, *2*) the complex nature of their underlying hematologic malignancy, *3*) the impact of immunosuppressive treatments, or *4*) a greater susceptibility to the harms associated with critical care (i.e., ventilator-associated lung injury, secondary infections, etc.)? Do we need a complete paradigm shift in our categorization and approach to respiratory failure and ARDS in this cohort? The right answer likely involves a combination of all these factors. In the crusade to improve HCT–ARDS outcomes, dedicated and rigorous studies evaluating this complex subgroup are needed.

In this issue of *AnnalsATS*, Herasevich and colleagues (pp. 1004–1012) report the results of a nested case-control study that sought to describe risk factors of ARDS following a first-time HCT using variables available before transplant (12). Among 3,920 patients who underwent HCT, 4.5% developed ARDS within 1 year of transplant. The analytic cohort consisted of 164 ARDS cases matched to 492 non-ARDS control subjects. Among patients that developed ARDS, 65% were categorized as severe, and the majority (69%) occurred in the first 100 days following the transplant. The underlying etiology for ARDS was classified as infectious (54%), peri-engraftment (16%), diffuse alveolar hemorrhage (2%), or undetermined (17%). The authors identified several pretransplant variables that were associated with the development of ARDS: worse pulmonary function, poor performance status, abnormal laboratory tests (albumin, aspartate aminotransferase, hemoglobin, platelets, and leukocytes), specific chemotherapeutic agents, radiation therapy, higher need of blood products, and prior hospital admission (requiring mechanical ventilation). All-cause mortality at 1 year was 70% in the ARDS cohort.

These risk factors have face validity and seem to perform well in different types of HCT (allogeneic and autologous) and for different time periods (before and after 100 d following HCT). The authors highlight the notion that given the high mortality rates observed across HCT–ARDS, a focus on prevention might be desirable. This study sheds light on which patients are more likely to develop this devastating complication with factors that are easily identifiable prior to transplant. The extent to which these variables are mere predictors or are causally associated with the development of ARDS cannot be clearly depicted from this analysis; however, the study establishes the groundwork for future research evaluating the pathophysiologic processes that render them more susceptible to ARDS. It also identifies a high-risk cohort in which the risk of ARDS can be discussed together with other risk factors for transplant-related morbidity and mortality at the time of initial consultation. This may also potentially inform advanced care planning discussions (13). The authors should be commended for putting together one of the largest contemporary cohorts of patients with HCT and describing early factors associated with the subsequent development of ARDS.

The complex puzzle of respiratory failure following HCT has multiple edges that still need to be further characterized. Although Herasevich and colleagues' work addresses the question of early identification of those at risk of ARDS, much work needs to be done in parallel to understand the mechanisms of ARDS in this population. The impact of immunosuppressive therapy in allogeneic transplant recipients and immunologic confounders such as graft versus host disease would also warrant further examination. Future research should further explore the physiologic links between these factors and ARDS and, perhaps most importantly, targeted interventions—when feasible—to decrease mortality.

Over the past 2 decades, significant efforts were made to achieve a common, simple, and pragmatic definition of ARDS to improve early identification (14). This, in turn, was meant to help with the adoption of life-saving evidence-based strategies that could be generally applied to a wide population (pressure and volume limited ventilation and prone positioning) (14, 15). However, have we gone too far in the oversimplification of ARDS—particularly across complex populations such as HCT? A recent observational study has even suggested that ARDS Berlin-severity categories defined by arterial oxygen tension/pressure to fraction of inspired oxygen thresholds may not carry the same prognostic weight in immunocompromised cohorts as it does in nonimmunocompromised patients (16). The HCT population has distinct time periods that correlate with distinct mechanisms of immunosuppression that render the recipient susceptible to unique causes of respiratory failure. Until we have a much clearer understanding of mechanisms, we may not be able to ameliorate mortality across those who develop ARDS. In this end, could the description of subphenotypes facilitate the depiction of the diverse respiratory syndromes occurring after HCT? Are there specific clinical and biologic factors that help differentiate infectious versus noninfectious complications? Do the same principles of management of ARDS apply to this specific population? How does neutropenic ARDS differ from nonneutropenic ARDS? And, finally, what is the impact that ARDS and mechanical ventilation have on short- and long-term outcomes in HCT recipients?

The study by Herasevich and colleagues is an important piece in the puzzle of respiratory failure following HCT and hopefully serves as a trigger for future research in the field. However, we must persist with a multipronged approach and continue to expand our understanding across the entire disease process. We must dive deeper back into pathophysiologic mechanisms of ARDS across this specific population in order to optimally understand the disease process driving mortality. In this case, less may not be more. ■

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References

1 Mokart D, Pastores SM, Darmon M. Has survival increased in cancer patients admitted to the ICU? Yes. *Intensive Care Med* 2014;40:1570–1572.
2 Azoulay E, Pène F, Darmon M, Lengliné E, Benoit D, Soares M, *et al*.; Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique (Grrr-OH). Managing critically Ill hematology patients: time to think differently. *Blood Rev* 2015;29:359–367.
3 Darmon M, Bourmaud A, Georges Q, Soares M, Jeon K, Oeyen S, *et al*. Changes in critically ill cancer patients' short-term outcome over the last decades: results of systematic review with meta-analysis on individual data. *Intensive Care Med* 2019;45:977–987.
4 Zampieri FG, Romano TG, Salluh JIF, Taniguchi LU, Mendes PV, Nassar AP Jr, *et al*. Trends in clinical profiles, organ support use and outcomes of patients with cancer requiring unplanned ICU admission: a multicenter cohort study. *Intensive Care Med* 2021;47:170–179. [Published erratum appears in *Intensive Care Med* 47:259–260.]
5 Lengliné E, Chevret S, Moreau AS, Pène F, Blot F, Bourhis JH, *et al*. Changes in intensive care for allogeneic hematopoietic stem cell transplant recipients. *Bone Marrow Transplant* 2015;50:840–845.
6 Afessa B, Peters SG. Major complications following hematopoietic stem cell transplantation. *Semin Respir Crit Care Med* 2006;27:297–309.
7 Hamidi M, Gossack-Keenan KL, Ferreyro BL, Angriman F, Rochwerg B, Mehta S. Outcomes of hematopoietic cell transplant recipients requiring invasive mechanical ventilation: a two-centre retrospective cohort study. *Can J Anaesth* 2019;66:1450–1457.
8 Guidelines for intensive care unit admission, discharge, and triage: task force of the American College of Critical Care Medicine, Society of Critical Care Medicine. *Crit Care Med* 1999;27:633–638.
9 Paz HL, Crilley P, Weinar M, Brodsky I. Outcome of patients requiring medical ICU admission following bone marrow transplantation. *Chest* 1993;104:527–531.
10 Braude S, Apperley J, Krausz T, Goldman JM, Royston D. Adult respiratory distress syndrome after allogeneic bone-marrow transplantation: evidence for a neutrophil-independent mechanism. *Lancet* 1985;1:1239–1242.
11 Munshi L, Darmon M, Soares M, Pickkers P, Bauer P, Meert AP, *et al*. (2020). Acute respiratory failure outcomes in patients with hematologic malignancies and hematopoietic cell transplant: a secondary analysis of the EFRAIM study. *Biol Blood Marrow Transplant* [online ahead of print] 2 Oct 2020; DOI: 10.1016/j.bbmt.2020.09.035.
12 Herasevich S, Frank RD, Bo H, Alkhateeb H, Hogan WJ, Gajic O, *et al*. Pretransplant risk factors can predict development of acute respiratory distress syndrome after hematopoietic stem cell transplantation. *Ann Am Thorac Soc* 2021;18:1004–1012.
13 Spring J, McKinlay J, Puxty K, Metaxa V, Detsky M, Mehta S, *et al*. Perspectives on advance care planning for patients with hematologic malignancies: an international clinician questionnaire. *Ann Am Thorac Soc* [online ahead of print] 5 Jan 2021; DOI: 10.1513/AnnalsATS.202006-678OC.
14 Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, *et al*.; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526–2533.
15 Fan E, Del Sorbo L, Goligher E, Hodgson CL, Munshi L, Walkey AJ, *et al*.; American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017;195:1253–1263. [Published erratum appears in *Am J Respir Crit Care Med* 195:1540.]
16 Demoule A, Antonelli M, Schellongowski P, Pickkers P, Soares M, Meyhoff T, *et al*. Respiratory mechanics and outcomes in immunocompromised patients with ARDS: a secondary analysis of the EFRAIM study. *Chest* 2020;158:1947–1957.

Predicting Incident Atrial Fibrillation Using Single Channel Nocturnal Oximetry: Can Necessity Become the Mother of Intervention?

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Obstructive sleep apnea (OSA) is fast becoming a global health crisis, with prevalence rates rising throughout the developed and developing world in parallel with the increasing prevalence of obesity (1). Several large, well-designed prospective cohort studies incorporating diverse groups of patients from around the world have consistently linked OSA with a greater burden of cardiovascular disease in general and with incident and prevalent atrial fibrillation (AF) in particular (2–5). These studies have shown that patients with OSA are more likely to develop AF and suffer more often from its consequences, such as stroke and premature death, than comparable subjects without OSA (6, 7). The argument that OSA may directly contribute to the development of AF is biologically plausible, and a growing body of basic science evidence points to hypoxemia and autonomic dysregulation, often manifested clinically through heart rate variability, as likely culprits (8, 9). Unfortunately, there are disparate levels of awareness of the relationship between OSA and AF between general practitioners, sleep medicine specialists, and cardiologists, and uniform guidelines for screening patients with OSA for AF (and vice versa) are lacking (10).

In an ideal world, all patients at risk for OSA would be appropriately screened and

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