

4. Famous KR, Delucchi K, Ware LB, Kangelaris KN, Liu KD, Thompson BT, *et al.*; ARDS Network. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. *Am J Respir Crit Care Med* 2017;195:331–338.
5. Calfee CS, Delucchi KL, Sinha P, Matthay MA, Hackett J, Shankar-Hari M, *et al.*; Irish Critical Care Trials Group. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. *Lancet Respir Med* 2018;6:691–698.
6. Antcliffe DB, Burnham KL, Al-Beidh F, Santhakumaran S, Brett SJ, Hinds CJ, *et al.* Transcriptomic signatures in sepsis and a differential response to steroids: from the VANISH randomized trial. *Am J Respir Crit Care Med* 2019;199:980–986.
7. Reddy K, Sinha P, O’Kane CM, Gordon AC, Calfee CS, McAuley DF. Subphenotypes in critical care: translation into clinical practice. *Lancet Respir Med* 2020;8:631–643.
8. Kitsios GD, Yang L, Manatakis DV, Nouraei M, Evankovich J, Bain W, *et al.* Host-response subphenotypes offer prognostic enrichment in patients with or at risk for acute respiratory distress syndrome. *Crit Care Med* 2019;47:1724–1734.
9. Sinha P, Calfee CS, Cherian S, Brealey D, Cutler S, King C, *et al.* Prevalence of phenotypes of acute respiratory distress syndrome in critically ill patients with COVID-19: a prospective observational study. *Lancet Respir Med* 2020;8:1209–1218.
10. Heijnen NFL, Hagens LA, Smit MR, Cremer OL, Ong DSY, van der Poll T, *et al.*; MARS Consortium. Biological subphenotypes of acute respiratory distress syndrome show prognostic enrichment in mechanically ventilated patients without acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2021;203:1503–1511.
11. Sinha P, Delucchi KL, McAuley DF, O’Kane CM, Matthay MA, Calfee CS. Development and validation of parsimonious algorithms to classify acute respiratory distress syndrome phenotypes: a secondary analysis of randomised controlled trials. *Lancet Respir Med* 2020;8:247–257.
12. Sinha P, Churpek MM, Calfee CS. Machine learning classifier models can identify acute respiratory distress syndrome phenotypes using readily available clinical data. *Am J Respir Crit Care Med* 2020;202:996–1004.
13. Bos LDJ, Scicluna BP, Ong DSY, Cremer O, van der Poll T, Schultz MJ. Understanding heterogeneity in biologic phenotypes of acute respiratory distress syndrome by leukocyte expression profiles. *Am J Respir Crit Care Med* 2019;200:42–50.
14. Wang Z, Gerstein M, Snyder M. RNA-Seq: a revolutionary tool for transcriptomics. *Nat Rev Genet* 2009;10:57–63.
15. Stuart T, Satija R. Integrative single-cell analysis. *Nat Rev Genet* 2019;20:257–272.

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⊗ The Intersection of Health and Critical Illness: Preservation and Restoration

Health is a state of “physical, mental, and social well-being” (1). Critical illness, by its nature, is a threat to all domains of health. Envision the innumerable patients laying in ICU beds across the world. As they fight serious illness, and their care teams rally to battle with them, their muscles atrophy. Their cognition falters. The fabric of their social well-being is torn apart.

Days (or weeks) later, those who survive will emerge from the hospital, in varied states of disability, to continue their recovery. What is the long-term fate of these survivors? Will their health—their physical, mental, and social well-being—be restored to live and thrive? Does long-term recovery vary by the type of serious illness that warrants ICU admission?

These and other fundamental questions have troubled us since Dr. Ramona Hopkins and colleagues published the experience of 55 acute respiratory distress syndrome survivors in 1999 (2). At 1 year, 78% exhibited impaired attention, concentration, memory, and/or mental processing speed, together with impairments in physical health, pain, and general health. Nearly half were unable to resume usual activities or return to work.

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In the decades after this wake-up call, an expansive body of literature has substantiated impairments in three domains—physical function, mental health, and cognition—after sepsis, respiratory failure, and other critical illnesses (3–5). Termed post-intensive care syndrome (PICS), this constellation of impairments after critical illness is remarkably common, and often severe and enduring (6, 7).

However, the epidemiology of PICS often lacked insight into patients’ baseline health before ICU admission. Given that “asteroid strikes are rare events in our medical ICUs,” accounting for pre-ICU health trajectory is vital to our understanding of long-term impairments (8). Furthermore, to personalize post-ICU care, a more mature understanding of impairments for the surgical population was warranted.

In this issue of the *Journal*, Geense and colleagues (pp. 1512–1521) provide important new insights into the trajectory of health in the year after critical illness (9). The investigators conducted a multicenter, longitudinal, prospective cohort study. The study enrolled adults admitted to medical and surgical ICUs from four hospitals in the Netherlands. Patients, or their proxies, completed baseline health questionnaires before elective surgery or during urgent surgical or medical ICU admissions. The investigators then obtained follow-up measures 1 year after ICU admission.

Assessments obtained in the pre-ICU and post-ICU period included measurement of frailty, fatigue, anxiety, depression, cognition, and quality of life. New or worsened physical function and post-traumatic stress symptoms were assessed at 1-year follow-up.

Of 3,320 patients who completed the baseline questionnaire, 2,345 (71%) completed the 1-year questionnaire. Most patients had an elective surgical admission (60%), whereas the remainder experienced medical (28%) or urgent surgical (12%) admissions.

Table 1. Opportunities to Prevent and Mitigate the Development of Long-Term Impairments after Critical Illness

Pre-ICU strategies to prevent critical illness	Public health measures (e.g., vaccination, masks) Population health efforts (e.g., education, housing) Optimize ambulatory care practices, including advance care planning, preventive measures (e.g., vaccination), and timely evaluation and management of ambulatory care-sensitive conditions (11)
ICU strategies	Standardize communication practices during critical illness (16), including introducing the concept of survivorship before ICU discharge Best practices to avoid preventable invasive mechanical ventilation (e.g., appropriate use of noninvasive positive-pressure ventilation, high-flow nasal cannula, early sepsis treatment) Assess, prevent, and manage pain Both spontaneous awakening trials and spontaneous breathing trials Choice of analgesia and sedation Delirium: assess, prevent, and manage Early mobility and exercise Family engagement and empowerment (e.g., ICU diary) (12) Functional reconciliation, wherein pre-ICU functional abilities are assessed and documented at ICU admission and reported, together with current functional abilities, during ICU to floor handoff
Post-ICU strategies	Hospital discharge functional impairment screening, linked to functional reconciliation, to inform post-acute care referral Engage post-acute care and ambulatory care setting to conduct after discharge screening assessment 2–4 wk after discharge Post-ICU clinics (15) Peer support groups

Importantly, most patients completed the baseline questionnaire themselves—75% of medical patients, 71% of urgent surgical patients, and 92% of elective surgical patients.

At 1 year, 43% of the elective surgical, 58% of the medical, and 64% of the urgent surgical patients had at least one new impairment in physical function, mental health, or cognition. The authors detailed a number of new or worsened physical impairments at 1 year post-ICU, ranging from weakness—the most common impairment—to uncommon symptoms such as loss of smell and swallowing difficulties. As may be expected, poorer pre-ICU health (e.g., anxiety, fatigue) was associated with an increased risk of long-term impairments. Conversely, consistent with recent work by Marra and colleagues (10), higher education level was associated with decreased risk of new physical, mental, or cognitive health problems.

The trajectory of impairments differed by type of admission, as did the ability to return to work. Specifically, urgent surgical patients experienced more new impairments across all PICS domains when compared with elective surgical patients, who actually experienced an improvement in physical and mental health on average. Among those employed, 34% of the elective surgical, 43% of the medical, and 54% of the urgent surgical patients were unable to return to full employment.

An important limitation of the study was the administration of baseline questionnaires during the ICU stay (by either patients or proxies), increasing the potential for recall bias. In addition, approximately 30% of patients were lost to follow-up. The loss to follow-up in a study of this nature may lead to overly optimistic estimates of recovery, as patients with severe impairments may be less likely to respond.

We must now consider how these lessons from Geense and colleagues can help us reduce the burden of long-term impairments

and restore health after the ICU. Fortunately, opportunities to preserve health exist across the spectrum of care (Table 1). For example, the striking contrast between outcomes after elective and urgent surgical ICU admissions raises questions of whether timely ambulatory care referral paired with access to care might preempt the development of urgent surgical indications. As for medical critical illness, a large claims-based study found that up to 15.8% of ICU admissions may be potentially preventable with optimal outpatient care for so-called ambulatory care-sensitive conditions (11). Together with public health measures, incorporated into ambulatory practice, the opportunity exists to reduce the growing population of ICU survivors by reducing the development of critical illness.

During ICU admission, beyond prioritizing the implementation of the ABCDEF bundle, the findings from Geense and colleagues harmonize well with recommendations from the Society of Critical Care Medicine's international consensus conference (12, 13). As summarized in Table 1, the consensus statement recommends the practice of functional reconciliation, coupled with serial, screening assessments to inform post-acute care referral and identify and rehabilitate new impairments after discharge. The recommended screening tools include many of the measures used in the current study, and provide an opportunity to standardize data across sites and studies. These include the Montreal Cognitive Assessment Test; Hospital Anxiety and Depression Scale; Impact of Event Scale-Revised (post-traumatic stress disorder); 6-minute-walk distance; and/or the EuroQol-5D-5L (health-related quality of life measure).

Health policy, and bundled payments, in particular, may serve as a catalyst to implement these recommendations. As post-acute care use (e.g., acute rehabilitation) varies by ICU type, future investigation is warranted to determine the optimal approach to rehabilitate identified

post-ICU impairments (14). Likewise, although conceptually appealing as a strategy to accelerate recovery, the value of post-ICU clinics and peer support groups for survivors requires further study (15).

In conclusion, the work by Geense and colleagues clarifies several fundamental questions of life after critical illness. By doing so, it lays the foundation toward a more coordinated health system designed to preserve and/or restore health through prevention of critical illness and more effective identification and rehabilitation of long-term impairments among survivors of critical illness. ■

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References

1. World Health Organization. WHO remains firmly committed to the principles set out in the preamble to the constitution. Geneva, Switzerland: WHO; 1946 [accessed 2021 Feb 4]. Available from: <https://www.who.int/about/who-we-are/constitution>.
2. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson-LOHR V. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999;160:50–56.
3. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010;304:1787–1794.
4. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al.; BRAIN-ICU Study Investigators. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306–1316.

5. Jackson JC, Pandharipande PP, Girard TD, Brummel NE, Thompson JL, Hughes CG, et al.; Bringing to light the Risk Factors And Incidence of Neuropsychological dysfunction in ICU survivors (BRAIN-ICU) study investigators. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. *Lancet Respir Med* 2014;2:369–379.
6. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med* 2012;40:502–509.
7. Maley JH, Brewster I, Mayoral I, Siruckova R, Adams S, McGraw KA, et al. Resilience in survivors of critical illness in the context of the survivors' experience and recovery. *Ann Am Thorac Soc* 2016;13:1351–1360.
8. Iwashyna TJ, Prescott HC. When is critical illness not like an asteroid strike? *Am J Respir Crit Care Med* 2013;188:525–527.
9. Geense WW, Zegers M, Peters MAA, Ewalds E, Simons KS, Vermeulen H, et al. New physical, mental, and cognitive problems 1 year after ICU admission: a prospective multicenter study. *Am J Respir Crit Care Med* 2021;203:1512–1521.
10. Marra A, Pandharipande PP, Girard TD, Patel MB, Hughes CG, Jackson JC, et al. Co-occurrence of post-intensive care syndrome problems among 406 survivors of critical illness. *Crit Care Med* 2018;46:1393–1401.
11. Weissman GE, Kerlin MP, Yuan Y, Kohn R, Anesi GL, Groeneveld PW, et al. Potentially preventable intensive care unit admissions in the United States, 2006-2015. *Ann Am Thorac Soc* 2020;17:81–88.
12. Ely EW. The ABCDEF bundle: science and philosophy of how ICU liberation serves patients and families. *Crit Care Med* 2017;45:321–330.
13. Mikkelsen ME, Still M, Anderson BJ, Bienvu OJ, Brodsky MB, Brummel N, et al. Society of Critical Care Medicine's international consensus conference on prediction and identification of long-term impairments after critical illness. *Crit Care Med* 2020;48:1670–1679.
14. Chesley CF, Harhay MO, Small DS, Hanish A, Prescott HC, Mikkelsen ME. Hospital readmission and post-acute care use after intensive care unit admissions: new ICU quality metrics? *J Intensive Care Med* [online ahead of print] 10 Sep 2020; DOI: 10.1177/0885066620956633.
15. Haines KJ, Sevin CM, Hibbert E, Boehm LM, Aparanji K, Bakhru RN, et al. Key mechanisms by which post-ICU activities can improve in-ICU care: results of the international THRIVE collaboratives. *Intensive Care Med* 2019;45:939–947.
16. Pasrich V, Gorman D, Laothamatus K, Bhardwaj A, Ganta N, Mikkelsen ME. Use of the serious illness conversation guide to improve communication with surrogates of critically ill patients: a pilot study. *ATS Scholar* 2020;1:119-133.

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⦿ The Future of Highly Effective Modulator Therapy in Cystic Fibrosis

The success of highly effective modulator therapy (HEMT) in cystic fibrosis (CF) now illustrates two areas of deficiency: the lack of

HEMT for younger children and for approximately 10% of the CF population without a qualifying mutation.

Inflammation, infection, and structural changes in the CF lung start in infancy or the early preschool years (1). Computed tomography scans of the chest and lung clearance index measurements are abnormal early and are not clearly associated with infection (1). The cardinal pulmonary lesion in CF, bronchiectasis, can be detected on chest computed tomography in up to 30–40% of children with CF aged between 3 and 4 years old with airway dilatation and thickening reported as early as the first few months of life (1). Linked to early inflammation are poor growth and nutrition.

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