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, Bienvenu 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.

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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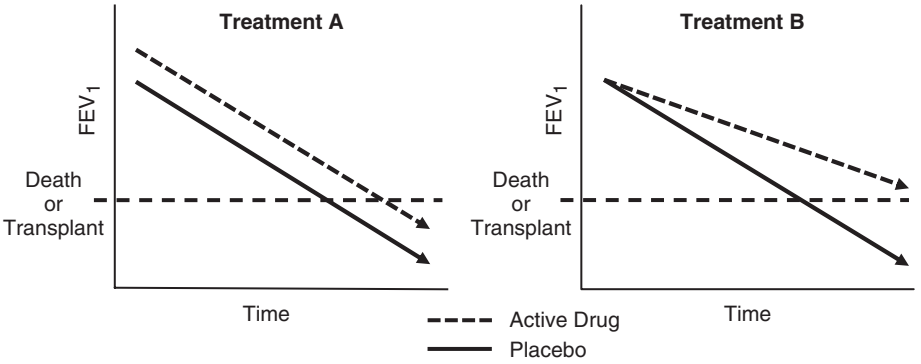

Figure 1. Schematic representation of two potential treatment responses. Treatment A acutely improves FEV_1 but does not slow rate of decline in FEV_1, resulting in a minor improvement in the long-term outcome. Treatment B does not acutely improve FEV_1 but does slow the rate of decline in FEV_1, resulting in sustained benefit.

Restriction of early lung growth worsens CF outcomes, but improvement in nutrition can ameliorate this (2). This evidence has led to an effort to bring effective therapies to infants and preschoolers with CF in an attempt to slow or stop progression. Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) targets the basic defect in CF by improving function of the native CFTR. It is hoped that early treatment with HEMT will mitigate this early disease progression, improve nutrition with a resultant improvement in lung growth, and change the course of CF over the lifetime. The urgency for early effective treatments for CF is real. Until we are able to address the basic defect in CF in the infant, we will likely continue to see significant morbidity because of this disease.

In this issue of the *Journal*, Zemanick and colleagues (pp. 1522–1532) share the results of a phase III clinical trial to prove safety and tolerability of ELX/TEZ/IVA in children aged 6 to 11 years (3). In this study, the open-label use of ELX/TEZ/IVA was studied in 66 children. The primary endpoint of the study was safety and tolerability, and the current article shows that the safety profile for ELX/TEZ/IVA in 6- to 11-year-old children was similar to the safety profile in older individuals (4, 5). The secondary endpoints were efficacy in terms of FEV_1 as well as reduction in sweat chloride, improvement in body mass index, and improvement in symptom scores. The coronavirus disease (COVID-19) worldwide epidemic occurred during the performance of this study. This epidemic had a global effect on clinical research, as the safety of participants in clinical trials took precedent over study visits and unnecessary exposures. Although adverse events were continuously collected for the entire study for participants, fewer participants had a full complement of efficacy measures. The intriguing data from those participants with efficacy endpoints at 24 weeks show a significant effect on both lung function (+10.2%) and sweat chloride levels (−60.9%). As is true for most pediatric studies, the starting lung function on average was normal. The lung function improvement was present despite this normalcy, even in the absence of a control group, suggesting significant efficacy, not just safety, in this age group. The 2-year open-label follow-up study will give more data on lung growth and disease progression. In addition, the weight-for-age *z*-score improved significantly from baseline, 0.37 versus −0.16. The authors contend that the reduction in sweat chloride deserves extra attention. All of the participants with two F508del alleles reduced their sweat chloride levels below the diagnostic level of 60 mmol/L, with 42.9% achieving normal levels <30 mmol/L. The authors suggest that this finding alone may indicate a true change in the paradigm of the future of CF in these children. Although individuals with mild CF mutations who have lower sweat chloride values have better outcomes, this may or may not be applicable to patients with pharmaceutically induced lower sweat chloride values. It is, however, intriguing and should spur the community to bring ELX/TEZ/IVA to the youngest individuals with CF as soon as possible. It is advantageous that the *a priori* design of this study was to have the primary outcome of safety. A study based on efficacy would have been significantly prolonged or not completed because of the COVID-19 crisis. Again, the 2-year follow-up study for these participants will be important to clarify both the impact and side effects of this therapy.

HEMF, such as IVA in individuals with gating mutations and ELX/TEZ/IVA in those with F508del, has been proven in pivotal phase III trials to significantly improve lung function, nutritional status, symptoms scores, and quality-of-life measures (4–6). It also significantly decreases sweat tests. Most importantly, however, HEMT decreases the incidence of pulmonary exacerbation (4, 5). Longer-term studies of modulators prove that there is a clear reduction in the rate of lung decline in individuals treated with these therapies. This reduction in the lung function decline for IVA is dramatic, from −8.3% to −0.7% using U.S. and U.K. registry data (7, 8). Although a therapy that improves lung function alone may improve longevity by a matter of years, a therapy that slows the rate of decline has an ongoing effect over the lifetime with a greater extension of life (Figure 1). ELX/TEZ/IVA appears to be a therapy that will do both and have the greatest long-term impact.

The efficacy of HEMT points out, however, the lack of available HEMT to a subset of people living with CF. Mutations that are not amenable to HEMT are more common in individuals of minority race and ethnicity, and this contributes to the poor outcomes in these groups (9, 10). In this study, only 1 of 66 participants was a minority. Fighting for equity for all individuals living with CF has become a main emphasis for the CF Foundation in terms of research, access, and outcomes.

At this point, the previous modulators IVA, lumacaftor/IVA, and TEZ/IVA have all been approved for younger ages than the original phase III qualifying studies (11, 12). IVA has recently been approved down to 4 months, whereas lumacaftor/IVA is approved to 2 years and TEZ/IVA is approved to 6 years (13–15). Longer-term data from these extensions show ongoing safety and efficacy even in the youngest patients (16, 17). Previous modulators have been shown to be safe, both in the short and long term, in young children. This knowledge should reaffirm the safety findings in the current study and should prove the appropriateness of moving

ELX/TEZ/IVA to the 6- to 11-year-old age group. The CF community has been waiting for the results of this study and to have ELX/TEZ/IVA for children. The goal and expectation will be much better long-term outcomes for people living with CF.

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References

1. Ranganathan SC, Hall GL, Sly PD, Stick SM, Douglas TA. AREST-CF. Early lung disease in infants and preschool children with cystic fibrosis. *Am J Respir Crit Care Med* 2017;195:1567–1575.
2. Sanders DB, Fink A, Mayer-Hamblett N, Schechter MS, Sawicki GS, Rosenfeld M, *et al*. Early life growth trajectories in cystic fibrosis are associated with pulmonary function at age 6 years. *J Pediatr* 2015;167:1081–8.e1.
3. Zemanick ET, Taylor-Cousar JL, Davies J, Gibson RL, Mall MA, McKone EF, *et al*.; VX18-445-106 Study Group. A phase 3 open-label study of elexacaftor/tezacaftor/ivacaftor in children 6 through 11 years of age with cystic fibrosis and at least one *F508del* allele. *Am J Respir Crit Care Med* 2021;203:1522–1532.
4. Heijerman HGM, KcKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, *et al*.; VX17-445-103 Study Group. Efficacy and safety of the elexacaftor/tezacaftor/ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomized, phase 3 trial. *Lancet* 2019;394:1940–1948.
5. Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, *et al*.; VX17-445-102 Study Group. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del allele. *N Engl J Med* 2019;381:1809–1819.
6. Davies JC, Wainwright CE, Canny GJ, Chilvers MA, Howenstine MS, Munck A, *et al*.; VX08-770-103 (ENVISION) Study Group. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. *Am J Respir Crit Care Med* 2013;187:1219–1225.
7. Bessonova L, Volkova N, Higgins M, Bengtsson L, Tian S, Simard C, *et al*. Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor. *Thorax* 2018;73:731–740.
8. Volkova N, Moy K, Evans J, Campbell D, Tian S, Simard C, *et al*. Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries. *J Cyst Fibros* 2020;19:68–79.
9. Rho J, Ahn C, Gao A, Sawicki GS, Keller A, Jain R. Disparities in mortality of Hispanic patients with cystic fibrosis in the United States. A national and regional cohort study. *Am J Respir Crit Care Med* 2018;198:1055–1063.
10. McGarry ME, McColley SA. Cystic fibrosis patients of minority race and ethnicity less likely eligible for CFTR modulators based on CFTR genotype. *Pediatr Pulmonol* [online ahead of print] 20 Jan 2021; DOI: 10.1002/ppul.25285.
11. Milla CE, Ratjen F, Marigowda G, Liu F, Waltz D, Rosenfeld M; VX13-809-011 Part B Investigator Group. Lumicaftor/ivacaftor in patients aged 6-11 years with cystic fibrosis and homozygous for F508del-CFTR. *Am J Respir Crit Care Med* 2017;195:912–920.
12. Walker S, Flume P, McNamara J, Solomon M, Chilvers M, Chmiel J, *et al*.; VX15-661-113 Investigator Group. A phase 3 study of tezacaftor in combination with ivacaftor in children aged 6 through 11 years with cystic fibrosis. *J Cyst Fibros* 2019;18:708–713.
13. Rosenfeld M, Wainwright CE, Higgins M, Wang LT, McKee C, Campbell D, *et al*.; ARRIVAL study group. Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. *Lancet Respir Med* 2018;6:545–553.
14. Davies JC, Wainwright CE, Sawicki GS, Higgins MN, Campbell D, Harris C, *et al*.; ARRIVAL Study Group. Ivacaftor in infants aged 4 to <12 months with cystic fibrosis and a gating mutation: Results of a two-part phase 3 clinical trial. *Am J Respir Crit Care Med* 2021;203:585–593.
15. McNamara JJ, McColley SA, Marigowda G, Liu F, Tian S, Owen CA, *et al*. Safety, pharmacokinetics, and pharmacodynamics of lumacaftor and ivacaftor combination therapy in children aged 2-5 years with cystic fibrosis homozygous for F508del-CFTR: an open-label phase 3 study. *Lancet Respir Med* 2019;7:325–335.
16. Rosenfeld M, Cunningham S, Harris WT, Lapey A, Regelmann WE, Sawicki GS, *et al*.; KLIMB study group. An open-label extension study of ivacaftor in children with CF and a CFTR gating mutation initiating treatment at age 2-5 years (KLIMB). *J Cyst Fibros* 2019;18:838–843.
17. Chilvers MA, Davies JC, Milla C, Tian S, Han Z, Cornell AG, *et al*. Long-term safety and efficacy of lumacaftor-ivacaftor therapy in children aged 6-11 years with cystic fibrosis homozygous for the F508del-CFTR mutation: a phase 3, open-label, extension study. *Lancet Respir Med* [online ahead of print] 28 Jan 2021; DOI: 10.1016/S2213-2600(20)30517-8.

NEDD9, a Hypoxia-upregulated Mediator for Pathogenic Platelet–Endothelial Cell Interaction in Pulmonary Hypertension

Pulmonary hypertension (PH) is a progressive cardiopulmonary syndrome with high mortality and poor prognosis. Excessive pulmonary vascular remodeling and fibrosis, due in part to the endothelium injury and platelet–endothelium interaction, is one of the major causes for elevated pulmonary vascular resistance and pulmonary arterial pressure in patients with PH and experimental animal models (1–3). Hypoxia and hemodynamic shear stress in the pulmonary vasculature are believed to activate thrombotic pathways, leading to the formation of *in situ* thrombosis in pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH) (4, 5). Emerging studies have reported the contribution of platelet activation in the formation of pulmonary vascular thrombosis and the development of pulmonary vascular remodeling. Upon activation, the platelets aggregate to the damaged pulmonary vasculature and release vasoactive mediators, angiogenic agents, growth factors, chemokines, and cytokines, many of which are implicated in the

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