these approaches may identify new, specific drug targets to modulate the host response to critical injury (15), and actionable estimates of individual treatment effect for critically ill patients. ■

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References

1. Arrowsmith J. Trial watch: phase II failures: 2008-2010. *Nat Rev Drug Discov* 2011;10:328–329.
2. Marshall JC. Why have clinical trials in sepsis failed? *Trends Mol Med* 2014;20:195–203.
3. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:801–810.
4. Davenport EE, Burnham KL, Radhakrishnan J, Humburg P, Hutton P, Mills TC, et al. Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. *Lancet Respir Med* 2016;4:259–271.
5. Sweeney TE, Azad TD, Donato M, Haynes WA, Perumal TM, Henao R, et al. Unsupervised analysis of transcriptomics in bacterial sepsis across multiple datasets reveals three robust clusters. *Crit Care Med* 2018;46:915–925.
6. Scicluna BP, van Vught LA, Zwinderman AH, Wiewel MA, Davenport EE, Burnham KL, et al.; MARS Consortium. Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study. *Lancet Respir Med* 2017;5:816–826.
7. Dunning JW, Merson L, Rohde GGU, Gao Z, Semple MG, Tran D, et al.; ISARIC Working Group 3, ISARIC Council. Open source clinical science for emerging infections. *Lancet Infect Dis* 2014;14:8–9.
8. 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.
9. Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot J-P, Siami S, et al.; CRICS-TRIGGERSEP Network. Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med* 2018;378:809–818.
10. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, et al.; ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group. Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 2018;378:797–808.
11. 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.
12. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA. Latent class analysis of ARDS subphenotypes: analysis of data from two randomized controlled trials. *Lancet Respir Med* 2014;2:611–620.
13. Russell CD, Baillie JK. Treatable traits and therapeutic targets: goals for systems biology in infectious disease. *Curr Opin Syst Biol* 2017;2:139–145.
14. Baillie JK, Bretherick A, Haley CS, Clohisey S, Gray A, Neyton LPA, et al.; IIBDGC Consortium. Shared activity patterns arising at genetic susceptibility loci reveal underlying genomic and cellular architecture of human disease. *PLoS Comput Biol* 2018;14:e1005934.
15. Baillie JK. Translational genomics: targeting the host immune response to fight infection. *Science* 2014;344:807–808.

Cardiopulmonary Exercise Testing: Another Tool in the Prognostication Tool Kit for Cystic Fibrosis

Survival for individuals with cystic fibrosis (CF) is improving over time, but progressive respiratory failure remains the number one cause of death for individuals with CF (1). Historically, $FEV_1 < 30\%$ of the predicted value has prompted discussions in CF clinics about the potential need for lung transplantation (LTx) (2, 3). However, survival with advanced lung disease is increasing over time, with a recent estimate of median survival of 6.6 years after $FEV_1 < 30\%$ in the United States (3–6). Despite the improved survival times for individuals with $FEV_1 < 30\%$, rates of death in the United States are approximately 10% per year after this lung function threshold is reached (6). Although FEV_1 has been shown to have a strong and consistent association with death or LTx in CF, there are other predictors as well, including malnutrition, hypoxemia, hypercarbia, pulmonary hypertension, increased frequency of exacerbations or hospitalizations, sputum culture positive for *Burkholderia cepacia*, massive hemoptysis, and reduced 6-minute-walk test distance (3, 4, 7–11). Despite these data, estimating the time until death or LTx in patients with CF is exceedingly difficult, and care teams need more and better tools to prognosticate in this patient population.

In this issue of the *Journal*, Hebestreit and colleagues (pp. 987–995) present a multicenter, international, retrospective study of clinically indicated cardiopulmonary exercise testing (CPET) for

individuals with CF (12). Ten centers (in Europe, Australia, and North America) contributed CPET data from over 500 individuals with CF, age ≥ 10 years, between 2000 and 2007. Data from a valid maximal CPET were available for 433 individuals, with follow-up of the cohort through 2014. The subjects selected were relatively healthy despite having a clinical indication for CPET (mean FEV_1, 73% predicted; 5-year survival rate, 93%). The investigators found that $\dot{V}O_{2peak}$, $work_{peak}$, $\dot{V}E/\dot{V}O_2$, and $\dot{V}E/\dot{V}CO_2$ were all associated with the composite outcome after adjustment for other known predictors of death and/or LTx in multivariable models. Using Ward's hierarchical clustering, the investigators identified four clusters, which included continuous and binary clinical and physiological parameters. This cluster analysis identified a group of individuals with low FEV_1, low body mass index z-scores, and worse CPET performance with dismal outcomes over the course of 10 years (63% death or LTx). Although FEV_1 was the most important variable for clustering, the CPET-derived parameters had a stronger influence on clustering than other traditional risk factors for death or LTx.

This study has several strengths. First, this is the largest study of CPET in CF, and it confirms prior single-center findings regarding the prognostic value of CPET-derived parameters in adults and adolescents with CF (13–15). Because of the large sample size in this study, analyses could be adjusted for important potential confounders of the association between CPET performance and death or LTx. The investigators identified strong relationships between CPET variables and death or LTx in the entire cohort that were independent of FEV_1, as well as among individuals with advanced lung disease ($FEV_1 < 40\%$) and in short-term (2 yr) sensitivity analyses. Second, this study had long-term follow-up of clinical outcomes, with very few individuals lost to follow-up or missing primary endpoint data 5 years or more after CPET ($n = 58$, excluded from analyses). Third, the use of cluster analysis highlights the importance of focusing prognostication on the highest-risk group (individuals with low FEV_1, malnutrition, and poor CPET performance). One of the key benefits of CPET is that it represents a functional and dynamic assessment of the cardiopulmonary system. Such an evaluation provides important clinical variables that are unavailable during a static test of airflow, such as office spirometry.

One of the fundamental challenges of prognosticating in CF is that the event rate (death or LTx) in the overall population is low. Prognostication is most relevant for individuals with an imminent risk of death, to avoid missing the opportunity for LTx in the appropriate individuals with CF. Incorporation of CPET could augment the complex decision-making that occurs around the timing of evaluation and listing for LTx. Interestingly, because of longstanding evidence of CPET-derived parameters (e.g., $\dot{V}O_{2peak}$ and $\dot{V}E/\dot{V}CO_2$ slope) as predictors of death in patients with systolic heart failure, the selection of heart transplant candidates has incorporated CPET for more than a decade (16), and carefully collected prospective data support the prognostic value of CPET for these individuals (17–19). The identification of threshold values for CPET parameters to guide the timing of listing individuals with CF for LTx could be invaluable because of the documented prolonged survival with low lung function and the poor positive predictive value of $FEV_1 < 30\%$ predicted (10).

Some key weaknesses of the study were acknowledged by the authors. One concern raised was the potential for confounding by CF center practices. They identified significant differences in outcomes at the CF center level. This in turn led the investigators to adjust for clinical site in their models. Although this analysis can take into account within-site correlation of participants, it cannot address potential differential indication bias. Individuals who underwent CPET at each site may have had different disease severities or clinical indications that could not be accounted for in the analysis. When indication bias occurs in an observational study, it remains a challenge to address analytically. The investigators would have needed a separate control population of individuals who had an equal probability (potentially via the propensity score) of undergoing CPET but did not receive the test. Differential outcome ascertainment is also a potential source of bias for this study, as the investigators attempted to minimize the risk of bias from loss to follow-up or informative censoring, but may have introduced ascertainment bias when the cohort was limited to individuals with a minimum of 5 years of follow-up at the testing CF center (e.g., healthier individuals may have moved away from the center). Thus, it remains challenging to generalize the results of this study to the greater CF population. Despite these limitations, the data presented provide strong observational evidence for the potential role of CPET in risk stratification for individuals with CF.

In conclusion, CPET adds prognostic information beyond the FEV_1 and could be a dynamic marker of disease progression in CF. The study by Hebestreit and colleagues is a call to action to perform a prospective study of CPET for individuals with CF—ideally, individuals with severe CF. CPET is another tool in the prognostication tool kit for CF and prospective research is imperative for individuals with advanced lung disease approaching LTx. ∎

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References

1. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation patient registry; 2017 annual data report [accessed 2018 Oct 30]. Available from: https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2017-Patient-Registry-Annual-Data-Report.pdf.
2. Ramos KJ, Somayaji R, Lease ED, Goss CH, Aitken ML. Cystic fibrosis physicians' perspectives on the timing of referral for lung transplant evaluation: a survey of physicians in the United States. *BMC Pulm Med* 2017;17:21.
3. Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. *N Engl J Med* 1992;326:1187–1191.
4. Milla CE, Warwick WJ. Risk of death in cystic fibrosis patients with severely compromised lung function. *Chest* 1998;113:1230–1234.
5. George PM, Banya W, Pareek N, Bilton D, Cullinan P, Hodson ME, et al. Improved survival at low lung function in cystic fibrosis: cohort study from 1990 to 2007. *BMJ* 2011;342:d1008.
6. Ramos KJ, Quon BS, Heltshe SL, Mayer-Hamblett N, Lease ED, Aitken ML, et al. Heterogeneity in survival in adult patients with cystic fibrosis with $FEV_1 < 30\%$ of predicted in the United States. *Chest* 2017;151:1320–1328.
7. Nkam L, Lambert J, Latouche A, Bellis G, Burgel PR, Hocine MN. A 3-year prognostic score for adults with cystic fibrosis. *J Cyst Fibros* 2017;16:702–708.
8. Stephenson AL, Tom M, Berthiaume Y, Singer LG, Aaron SD, Whitmore GA, et al. A contemporary survival analysis of individuals with cystic fibrosis: a cohort study. *Eur Respir J* 2015;45:670–679.
9. Belkin RA, Henig NR, Singer LG, Chaparro C, Rubenstein RC, Xie SX, et al. Risk factors for death of patients with cystic fibrosis

awaiting lung transplantation. *Am J Respir Crit Care Med* 2006;173: 659–666.

10. Mayer-Hamblett N, Rosenfeld M, Emerson J, Goss CH, Aitken ML. Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality. *Am J Respir Crit Care Med* 2002;166:1550–1555.

11. Martin C, Chapron J, Hubert D, Kanaan R, Honoré I, Paillasseur J-L, *et al*. Prognostic value of six minute walk test in cystic fibrosis adults. *Respir Med* 2013;107:1881–1887.

12. Hebestreit H, Hulzebos EHJ, Schneiderman JE, Karila C, Boas SR, Kriemler S, *et al*. Cardiopulmonary exercise testing provides additional prognostic information in cystic fibrosis. *Am J Respir Crit Care Med* 2019;199:987–995.

13. Hulzebos EH, Bomhof-Roordink H, van de Weert-van Leeuwen PB, Twisk JW, Arets HG, van der Ent CK, *et al*. Prediction of mortality in adolescents with cystic fibrosis. *Med Sci Sports Exerc* 2014;46:2047–2052.

14. Tantisira KG, Systrom DM, Ginns LC. An elevated breathing reserve index at the lactate threshold is a predictor of mortality in patients with cystic fibrosis awaiting lung transplantation. *Am J Respir Crit Care Med* 2002;165:1629–1633.

15. Moorcroft AJ, Dodd ME, Webb AK. Exercise testing and prognosis in adult cystic fibrosis. *Thorax* 1997;52:291–293.

16. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, *et al*.; International Society for Heart Lung Transplantation (ISHLT) Infectious Diseases Council; International Society for Heart Lung Transplantation (ISHLT) Pediatric Transplantation Council; International Society for Heart Lung Transplantation (ISHLT) Heart Failure and Transplantation Council. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant* 2016; 35:1–23.

17. Poggio R, Arazi HC, Giorgi M, Miriuka SG. Prediction of severe cardiovascular events by VE/VCO2 slope versus peak VO2 in systolic heart failure: a meta-analysis of the published literature. *Am Heart J* 2010;160:1004–1014.

18. Chua TP, Ponikowski P, Harrington D, Anker SD, Webb-Peploe K, Clark AL, *et al*. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol* 1997;29:1585–1590.

19. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991;83:778–786.

Does Breathing Wood Smoke Make the Flu Worse? Sex Might Matter

We all know influenza can be bad. Aside from the fevers, cough, miserable body aches, and severe fatigue, people can actually die from it. Pregnant women, young children, and the elderly are most at risk for mortality. Recent modeling estimates (1) suggest the global mortality from seasonal influenza has been previously underestimated. From 1999 to 2015, influenza accounted for as many as 645,000 annual excess respiratory deaths, with likely many additional circulatory deaths. The highest mortality rates occurred in sub-Saharan Africa and Southeast Asia in people older than 75 years.

Air pollution can also be bad, especially in developing countries. According to the World Health Organization, ambient air pollution caused 4.2 million premature deaths in 2016, with 91% of these in low- and middle-income countries (2). This does not include the health risks for the approximately 3 billion people that cook or heat their homes with kerosene, coal, and biomass fuels, including wood.

But what if air pollution takes influenza from bad to worse? This could mean that air pollution is increasing influenza mortality, in addition to its own significant mortality. In this issue of the *Journal*, Rebuli and colleagues (pp. 996–1007), in their clinical study (3), addressed the question of whether exposure to wood smoke worsens epithelial mucosal responses to influenza virus infection. Their experimental model is nasal inoculation with the influenza virus vaccine, which is a mixture of live attenuated influenza viruses (LAIV), followed by nasal lavage. Thirty-nine healthy men and women were randomly exposed for 2 hours at rest to filtered air or wood smoke, followed by LAIV inoculation. Nasal lavage was performed before and 1 and 2 days after exposure/viral challenge, with

assessment of changes in the expression of 255 genes and 30 cytokine proteins involved in inflammation. The researchers also assessed expression of viral genes as markers of infection and replication.

LAIV infection caused the expected changes in inflammatory gene expression, including the expression of viral genes, confirming infection and replication. Surprisingly, the primary analysis showed no significant wood smoke effects on any of the 255 inflammatory response genes. Only IP-10 (IFN-γ–induced protein 10 kDa) and IL-6 increased after LAIV; wood smoke partially suppressed the increase in IP-10.

However, in a planned secondary analysis, sex interacted significantly with exposure for 25 genes. Subsequent sex-specific analyses confirmed sex differences in gene expression before exposure, and in response to wood smoke. Many more genes were upregulated in men than in women before exposure. In the subjects exposed to filtered air followed by LAIV, women showed a more robust response than men. In the 8 men exposed to wood smoke compared with the 9 men exposed to filtered air, 13 genes increased expression more than twofold. In the 12 women exposed to wood smoke compared with 10 exposed to filtered air, 18 genes were differentially expressed, all downregulated, mostly less than twofold. Thus, the men had more inflammatory gene expression than women at baseline, with some genes increasing further with wood smoke and LAIV. Women had reduced gene expression at baseline, increased responses to filtered air/LAIV, and slight suppression of responses after wood smoke/LAIV. These wood smoke changes in opposite directions explain the negative outcome in the primary aggregate analysis.

Sometimes we fail to consider the possibility of sex differences in the design of clinical studies, including previous studies of wood smoke exposure (4), and Rebuli and colleagues make an important contribution in this regard. The biological differences between men and women may affect their responses to a variety of environmental insults, including air pollutants and influenza virus. Men and women differ in their ability to control a long list of viral infections, including influenza virus, and mortality from viral infections is generally greater in men