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Genetic Discovery, Rigorous Statistics, and Pandemic Influenza

Pandemic influenza threatens public health globally.¹ The pandemic 2009 influenza A(H1N1) (A[H1N1]pdm09) caused serious morbidity and high case-fatality rates worldwide: 214 countries reported 18,837 deaths during the first 6 months of 2010.² Patients with chronic medical conditions were especially prone to poor outcomes,^{3,5} but this strain of influenza, similar to the 1918 “Spanish” influenza virus in both genetic sequence⁶ and behavior,⁷ caused unusually severe effects in young adults. A(H1N1)pdm09 has the additional distinction of producing poor outcomes among pregnant^{3,4} and obese patients,⁸ a phenomenon not seen with other recent strains of influenza.

Rapid viral mutation of influenza viruses fuels well-founded fear focused on our inability to control pandemic disease. The 1918 influenza pandemic virus appears to have had an avian origin with specific mutations that conferred high transmissibility and lethality among humans.⁹ In contrast, A(H1N1)pdm09 resulted from multiple genetic reassortments of swine-origin influenza.

In this issue of *CHEST* (see page 1237), To et al¹⁰ highlight the importance of another component of disease severity, the host response to the pandemic virus isolated from patients in Hong Kong.¹¹ They explore the impact of genetic variation in surfactant B genes on human host responses to influenza and the resultant clinical severity of disease that so frequently causes death from influenza.

Our understanding of surfactant biology is evolving quickly. Surfactants have a host of roles and qualify as members of the growing number of known “moonlighting” proteins.¹² Evidence demonstrates that surfactants, including surfactant B, once thought to be primarily responsible for function hysteresis, influence

multiple pulmonary processes, including the development of pulmonary fibrosis¹³ and COPD.¹⁴ Surfactants A and D are well documented as playing a role in bacterial, fungal, and viral defense.¹⁵ Surfactant B is less well known for its immune properties but now looks to play a critical role in viral defense.

Genetic variation impacts protein structure and the ability of these proteins to perform any one or multiple of their functions. The common variants in our population are gradually being revealed to influence human variable response to disease and environmental stressors. The C allele of single nucleotide polymorphism (SNP) rs1130866 is the common allele, present in 70% of the Han Chinese population studied.¹⁶ It is this dominant variant that deleteriously influences the host response to viral infection and provides some insight into the variance in host response to a common but deadly virus. The minor allele appears to be protective in this specific setting.

Genetic variation is only one of many potential factors that can alter clinical outcomes of disease. Rigorous statistical procedures can and should facilitate discovery of those factors and highlight their relative importance. Successful statistical analysis can produce results that identify the most important features of disease for further clinical investigations, guide development of new treatments, and provide deeper insights into disease mechanisms. Using modern technology, To et al¹⁰ followed an old path to discovery: formulation of a testable hypothesis, evaluation one by one for univariate statistical associations between potential predictors and outcomes, and, finally, meticulous assessment of the relative importance of potentially independent contributors to the chosen outcome.

Specifically, they hypothesized that surfactant protein genetic variation may influence outcomes in influenza. They evaluated a chosen set of SNPs, searching plausible candidates related to surfactant proteins for an association with severe disease within rigorously controlled conditions. Finally, they assessed the significance of univariate relationships in a more diverse and, therefore, more generalizable group of subjects by means of multivariate analysis to find the relative importance of their selected SNP compared with other independent, potentially causal factors for severe disease. Hypothesis-driven exploration, carefully corrected for multiple comparisons, produced a borderline *P* value, above the arbitrary threshold of .05. But the hypothesis-driven nature of the study allowed a thoughtful interpretation that identified the SNP as worthy of additional investigation. Multivariate analysis within a larger population of patients replicated the real-world mix of young and old patients with chronic pulmonary, neurologic, cardiac, metabolic, and endocrine disorders and demonstrated true significance.

The multivariate analysis provides three important insights. First, a specific variation in surfactant protein B caused by an SNP, rs1130866, independently affects outcomes for a wide range of patients infected by A(H1N1)pdm09. Second, although obesity played the largest single role in determining severity in their study,⁸ To et al¹⁰ show that the genetic variation associated with surfactant B has an effect on severity comparable in strength to the effects of the other previously discovered major conditions that predispose to poor outcomes with influenza A infection.³ Finally, they show with specific testing that rs1130866 has no association with obesity, clearly showing the independence of their major finding.

The evidence presented by To et al¹⁰ provides an additional starting point for studies of mechanisms of pulmonary disease related to the role of surfactant proteins. The strong association of surfactant B with severe responses to infection suggests that further bench investigations might focus on the interaction of surfactants with A(H1N1)pdm09 viral particles.

Perhaps closer to the bedside, their results may help identify a subset of adult patients with acute lung injury and ARDS, an unfortunately common feature of A(H1N1)pdm09 infection,³ who might respond to surfactant therapy. Surfactant therapy fails in adult acute lung injury/ARDS but successfully treats infant respiratory distress syndrome; it is theorized that failure to detect efficacy in adults may be caused by patient heterogeneity.¹⁷ With additional data, patients with the common rs1130866 variant suffering ARDS from influenza A infection may prove to be one specific group of patients for whom surfactant therapy may be helpful.

Formulation of a specific testable hypothesis, rigorous study design, careful statistical analysis, and equally careful interpretation of results provide a secure basis for conducting science.¹⁸ In this case, To et al¹⁰ convincingly show that variation in rs1130866 has a clinically relevant impact on the severity of infection with influenza A in a general population of Chinese patients.

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Study Review Committee of the US Cystic Fibrosis Foundation (CFF); he is a recent past member of the Thoracic Committee of the United Network for Organ Sharing/Organization for the Procurement and Transplantation Network, the CFF Patient Registry Data Use Committee, the REVEAL Steering Committee (sponsored by Actelion Pharmaceuticals Ltd), and the National Institute for Occupational Safety and Health World Trade Center Research Review Committee. He has received grant funding from CFF Therapeutics, Inc; the NIH/NHLBI; and the Margolis Family Foundation of Utah; and receives funding for studies of therapies from CFF Therapeutics, Inc; Genentech Inc; Gilead Sciences, Inc; Inspire; MPex Pharmaceuticals, Inc; Savara Pharmaceuticals; and Vertex. He is a consultant for Gehrson Lehman Group, Inc; Genentech Inc; and Vertex.

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Expert Consensus on Advanced Critical Care Echocardiography

Opportunity to Do It Right

These are exciting times for echocardiography in the ICU. Several factors, including the following, have combined to produce a boom: high-quality ultrasound devices are commonplace in the ICU, increasing numbers of intensivists and fellows have sought out specialized training in critical care ultrasonography and echocardiography, echocardiography regularly reveals findings that complement more traditional measures of hemodynamic status, and intensivists have learned that personally integrating echocardiography into clinical assessment and treatment improves the traditional cardiologist-consultant model of formal echocardiography.¹ Basic critical care echocardiography (BCCE) is goal oriented, seeks to answer a limited number of clinical questions, uses five basic views (parasternal long- and short-axis, apical four-chamber, subxiphoid, and inferior vena caval), and should be required training for all intensivists.² On the other hand, advanced critical care echocardiography (ACCE) requires a comprehensive evaluation of cardiac anatomy and physiology, includes additional views and techniques (including transesophageal echocardiography [TEE] and Doppler), and, because it requires substantial additional training, is optional for the intensivist.² ACCE addresses a broader range of clinical questions than does BCCE, such as those surrounding regional ventricular function, valvular assessment, measurement of pressures and flows, diastolic function, tamponade, aortic dissection, and many others.

Will intensivists embrace ACCE? Like cardiac anesthesiologists in the operating room, intensivists are uniquely qualified to apply ACCE because of the nature of their work. Take, for example, management of the patient with severe ARDS. Good evidence shows that clinically significant right ventricular dysfunction is

common and that echocardiography (both via transthoracic and TEE approaches), yields images that show whether right ventricular dysfunction is present, how severe it is, and how it responds to interventions in real time.³⁻⁵ Moreover, modest changes in ventilator settings, blood gas values, vasoactive medications, fluid infusions, or even body positioning can provoke hemodynamic deterioration in ways that would be difficult to judge, monitor, or respond to without ACCE. One can readily imagine that intensivist-conducted echocardiography, especially when this includes advanced capabilities, will alter management and improve outcomes at modest cost and little risk. It seems self-evident that the future is bright.

But perhaps this is a good time to recall the history of the adoption of the pulmonary artery catheter (PAC) by intensivists. Pressure tracings of the right side of the heart, insight into left-sided heart function through the pulmonary artery occlusion pressure, accurate estimates of cardiac output, and chamber-specific oxyhemoglobin saturation values promised to guide management of the critically ill and save patients with shock, ARDS, and failing hearts. But it did not work out that way. In the ensuing decades, we learned that obtaining valid data was not simple,⁶ physicians could not agree on how to translate the data into a plan,⁷ and accurate data and explicit protocols simply failed to lead to the expected benefits.⁸ No doubt some of this can be blamed on intensivists' woeful lack of knowledge regarding the PAC.⁹ Haphazard training may have played a role. There were wide variations in what was taught, how much experience was expected before independent practice, and how competency was judged (if at all). If we could start all over again, we would surely begin with a curriculum, incorporate rigorous methodology into the training of fellows and practicing physicians, document competence rigorously, and then conduct clinical trials.

This editorial coincides with the publication of an International Expert Consensus Statement on ACCE.¹⁰ Professional societies from Europe, Asia, Australia, and North America, including the American College of Chest Physicians, contributed to and have endorsed the statement. The document builds on the foundation of two prior consensus publications regarding the competencies² and training standards¹¹ for critical care ultrasound and BCCE. Like them, the new statement describes, in rich detail, what is expected of physicians wishing to incorporate advanced echocardiographic techniques, including TEE, into ICU practice. Comprehensive tables list the views, qualitative and quantitative assessments, clinical questions, and requirements for faculty teaching ACCE. A detailed scoring system to judge competency is proposed. A particular strength of the statement is its emphasis on judging formal competence, including a specific instrument for testing. The authors conclude that, unlike for general critical