than women (5). Humoral and cellular antiviral immune responses are stronger in women. However, this could also increase aberrant responses such as autoimmunity in women relative to men. Ghosh, and colleagues (5) have reviewed the mechanisms involved for these sex-related differences. Of course there are the hormonal influences. And it turns out that many immune response genes are encoded on the X chromosome. One of the two X chromosomes is inactivated in female cells. Thus, a loss-of-function mutation in one of these X-linked immune response genes would be expressed in one-half of the cells in women, but all the cells in men, resulting in increased X-linked immunodeficiency in men.

We know that inflammation can be both good and bad. Good is controlling infection; bad is contributing to the symptoms and tissue damage in influenza. Although men are less able than women to mount an immune defense against the influenza virus, the findings of Rebuli and colleagues suggest that men have increased expression of inflammation-related genes in the nasal mucosa relative to women at baseline, and further increase inflammatory gene responses to LAIV infection with prior exposure to wood smoke. Thus, men have more difficulty than women in fighting off influenza, and prior wood smoke exposure may enhance the inflammatory response, and hence the severity, of influenza.

There are important limitations to this study. We do not know the degree to which the sex differences in gene expression observed by Rebuli and colleagues in response to wood smoke and LAIV are the result of shifts in the type of cells recovered from the nose. We are not provided with a differential cell count for the nasal lavage, but it is likely that the observed changes in gene expression reflect in part an influx of inflammatory cells into the nose in response to these combined challenges, rather than just changes in gene expression of resident nasal epithelial cells.

Also, it needs to be kept in mind that this study was not optimally designed to examine sex differences. Such a study would ideally include equal and sufficient numbers of men and women, with restricted, balanced randomization by sex to wood smoke versus filtered air. Perhaps the biggest problem is the relatively small number of subjects in each exposure group; for example, 8 men exposed to wood smoke and 9 to filtered air. This increases the possibility of spurious results that may not hold up in a larger study. Thus, these findings should be considered hypothesis generating, and not definitive.

Despite these limitations, Rebuli and colleagues have made important contributions to our understanding of interactions among a pollutant exposure, influenza virus infection, and sex. Their data remind us that males differ from females, sometimes with opposing effects that may "cancel" each other in aggregate analyses. Sex needs to be considered in study design, especially with regard to immune and inflammatory responses. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Mark W. Frampton, M.D.
University of Rochester School of Medicine
Rochester, New York

ORCID ID: 0000-0002-6002-2119 (M.W.F.).

References

1. Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, *et al*.; Global Seasonal Influenza-associated Mortality Collaborator Network. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet* 2018;391:1285–1300.
2. World Health Organization. Ambient (outdoor) air quality and health. 2018 May 2, 2018 [accessed 2018 Oct 22]. Available from: http://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health.
3. Rebuli ME, Speen AM, Martin EM, Addo KA, Pawlak EA, Glista-Baker E, *et al*. Wood smoke exposure alters human inflammatory responses to viral infection in a sex-specific manner: a randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2019;199:996–1007.
4. Ghio AJ, Soukup JM, Case M, Dailey LA, Richards J, Berntsen J, *et al*. Exposure to wood smoke particles produces inflammation in healthy volunteers. *Occup Environ Med* 2012;69:170–175.
5. Ghosh S, Klein RS. Sex drives dimorphic immune responses to viral infections. *J Immunol* 2017;198:1782–1790.

A New Tool to Capture Patients' Perceptions of the Effects of Lung Transplantation

For patients with many incurable, life-shortening lung conditions, lung transplantation offers "curative" therapy and the only therapeutic option with a reliable chance to improve their quality of life (QOL). But what is really meant by the term "QOL," and how do we measure this abstract construct?

For individuals, QOL refers to their perceptions of how well their needs and wants are met across dimensions of life that matter most to them. Thus, accurate assessments of QOL require knowledge of patients' perceptions, their needs and wants, and the dimensions of life they care about. Carefully crafted questionnaires, developed with systematically collected input from patients with the condition of interest, can capture all these things.

Until now, investigators and other stakeholders interested in examining the effect of lung transplantation on a person's QOL have had to rely on existing questionnaires (1–3). However, none of those questionnaires adequately address all of the domains that

Supported in part by grants from the Munn Foundation and the Clarence V. Laguardia Foundation.

Originally Published in Press as DOI: 10.1164/rccm.201810-2001ED on November 20, 2018

are important to patients after lung transplantation, including, among other things, emotional well-being, pulmonary and extrapulmonary symptoms, effects of immunosuppression, and neurocognitive status. In fact, some experts say that many existing questionnaires—even ones that call themselves "QOL" or "health-related QOL" questionnaires—are really measures of health status. They measure certain domains (and do it well), but by confining themselves to assessing physical and/or emotional health, they fail to capture other domains that contribute to a person's QOL, including physical and emotional well-being as well as material comforts; relationships with a spouse/partner, family, and friends; being able to help other people; learning; independence; working; understanding oneself; expressing oneself; and socializing (4, 5).

In this issue of the *Journal*, Singer and colleagues (pp. 1008–1019) describe the development and initial testing of a questionnaire that aims to assess QOL after lung transplantation (6). Rather than developing their own items *de novo*, these lung transplant and questionnaire-development experts used clusters of items from existing questionnaires to capture aspects of life after lung transplant. They initially identified 126 items comprising clusters from eight questionnaires. Next, they conducted 43 cognitive interviews with lung transplant recipients who were asked whether the words and grammar used for individual items were clear, and whether there was redundancy in the items or clusters. For clusters that tapped the same construct (e.g., respiratory symptoms), interviewees were asked to select which item cluster more clearly reflected their definition of health-related QOL. Forty-two items were dropped after the interviews, leaving 84 items for field testing. Results from an exploratory factor analysis led the investigators to drop another 24 items. This left their questionnaire, which they call the Lung Transplant Health-Related Quality of Life (LT-QOL) survey, with 60 items comprising 10 scales (pulmonary symptoms, gastrointestinal symptoms, neuromuscular symptoms, treatment burden, worry about future health, cognitive limitations, sexual problems, anxiety/depression, health distress, and general QOL).

Analyses showed that the LT-QOL has acceptable-to-excellent psychometric properties, ranging from internal consistency to floor and ceiling effects. In support of its validity, its scores correlated in expected directions with relevant domains from other questionnaires completed in the same sitting. Its scores also correlated, as hypothesized, with concurrently collected spirometric and walk-test data, and LT-QOL scores were significantly worse for respondents with severe chronic lung allograft dysfunction than for those without. These analyses suggest that the LT-QOL is a reliable questionnaire, and it would seem to assess domains that are meaningful to patients after lung transplantation. In short, it has easily passed the first psychometric hurdle. In my opinion, the methods used to develop this questionnaire were sound, and the numerous cognitive interviews with patients in the target population ensure its relevance.

The LT-QOL has some limitations, and there is more work to be done on it. Although the authors describe how the LT-QOL is more comprehensive than existing questionnaires, its 10 scales cover only five broad constructs: *1*) physical health, *2*) emotional/mental health, *3*) treatment burden, *4*) sexual health, and *5*) general QOL. Measurement experts may argue that the LT-QOL does not measure health-related QOL. As alluded to above, inquiring about the frequency or intensity of symptoms (physical or emotional/mental) gets at health status, but that line of inquiry is subtly different from specifically asking how much those symptoms—or the condition in all its aspects—affects the full spectrum of life domains that feed into QOL. I would call the LT-QOL a hybrid health-status/QOL questionnaire developed specifically for the post–lung transplant population. Its last two items—which I really like ("I am able to enjoy life" and "I am content with the quality of my life right now")—tap general QOL, but even they do not reveal whether or how the transplant (and all it involves and impacts) has affected the respondent's QOL or ability to enjoy life. It is important to emphasize what makes this questionnaire distinct, as I suspect many investigators who will use the LT-QOL will not have expertise in measurement and will not review its content in detail. Typically, they would, I suspect, see its name and assume it captures a comprehensive view of QOL after lung transplantation. They should know what they're getting by using it.

There may be some hidden redundancy in the LT-QOL: 10% (n = 6) of the items (from three different scales) include the term "worry," "worried," or "worrying" (e.g., "I worry that my lung transplant will not work . . . about getting infections . . . that my health will get worse . . . about not being able to stop or control worrying," "worrying too much about different things," and "is health a worry in your life?"). But redundancy only lengthens the questionnaire; it does not detract from its psychometric soundness.

This work suggests that the LT-QOL is a nice new tool that is capable of capturing patients' perceptions of the effects of lung transplantation, and it provides a foundation upon which to conduct additional analyses to support the validity of this tool. Remember that establishing the validity of a questionnaire is an ongoing process, not a threshold phenomenon, and involves using well-formulated hypotheses to test that questionnaire in many studies, under multiple conditions, to understand what its scores are able to reveal about respondents. The LT-QOL is primed and ready for use in observational and interventional studies. The investigators have placed the LT-QOL in the public domain, so others are free to use it. They suggest administering a generic QOL questionnaire alongside it. The next phase of analyses should assess how the LT-QOL tracks the post–lung transplant course, establish its responsiveness to changes in health status as time passes after transplantation, and determine its sensitivity for detecting differences in the health-status/QOL trajectory between groups over time. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Jeffrey J. Swigris, D.O., M.S.
Interstitial Lung Disease Program
National Jewish Health
Denver, Colorado

References

1. Finlen Copeland CA, Vock DM, Pieper K, Mark DB, Palmer SM. Impact of lung transplantation on recipient quality of life: a serial, prospective, multicenter analysis through the first posttransplant year. *Chest* 2013;143:744–750.
2. Singer JP, Katz PP, Soong A, Shrestha P, Huang D, Ho J, *et al*. Effect of lung transplantation on health-related quality of life in the era of the lung allocation score: a U.S. prospective cohort study. *Am J Transplant* 2017;17:1334–1345.

3. Singer LG, Chowdhury NA, Faughnan ME, Granton J, Keshavjee S, Marras TK, *et al*. Effects of recipient age and diagnosis on health-related quality-of-life benefit of lung transplantation. *Am J Respir Crit Care Med* 2015;192:965–973.
4. Burckhardt CS, Woods SL, Schultz AA, Ziebarth DM. Quality of life of adults with chronic illness: a psychometric study. *Res Nurs Health* 1989;12:347–354.
5. Flanagan J. A research approach to improving our quality of life. *Am Psychol* 1978;33:138–147.
6. Singer JP, Soong A, Chen J, Shrestha P, Zhuo H, Gao Y, *et al*. Development and preliminary validation of the Lung Transplant Quality of Life (LT-QOL) survey. *Am J Respir Crit Care Med* 2019;199:1008–1019.

Pulmonary Vascular Disease in Premature Infants
Early Predictive Models of Late Respiratory Morbidity

Pulmonary vascular disease (PVD) and established pulmonary hypertension (PH) are common associations of bronchopulmonary dysplasia (BPD) (1). Although the reported incidence of PH is 14–44% in infants with recognized BPD (2, 3), recent evidence indicates that up to 20% of extremely low gestational age neonates without BPD will develop some degree of PVD during the neonatal period (2, 3). The mechanistic interrelation of both pathologies in more prematurely born infants is informed by the tandem development of the alveoli and microvasculature (4). BPD and PH share similar risk factors and overlapping symptoms, with some pointing to early PVD as an essential causative factor in the pathobiology of BPD (2) and others suggesting that PVD could be a distinct feature of prematurity, rather than a manifestation of BPD (5–7). Regardless of its association with BPD, it is more likely that PVD is just one of many factors leading to impaired respiratory function after preterm birth. It is not surprising that early identification of PVD, independent of the diagnosis BPD, may predict later pulmonary dysfunction, especially because preterm birth is associated with an increased risk of PH in childhood, adolescence, and adulthood (8).

Improved echocardiographic assessment of PVD has led to increased recognition that disrupted pulmonary vascular growth in preterm infants may contribute to the pathogenesis of late respiratory disease (LRD) (2, 7). The diagnosis of PVD and the true prevalence of PH in preterm infants has been difficult to discern because of the paucity of reliable noninvasive measures to evaluate pulmonary hemodynamics (1) and an underappreciation for the practice of screening for PVD in extremely low gestational age neonates, with a focus primarily on infants with BPD (9). However, preterm infants without a diagnosis of BPD also remain at risk for respiratory morbidities and abnormal lung function into childhood, emphasizing the need to focus on alternate measures that explore differing mechanisms of disrupted pulmonary vascular and airway growth after prematurity (10).

In this issue of the *Journal*, Mourani and colleagues (pp. 1020–1027) leveraged a multicenter cohort of preterm infants to demonstrate that echocardiographic evidence of PVD at 7 days of age was associated with a higher incidence of LRD in early childhood (11). This builds on their previous report demonstrating that early echocardiographic findings of PVD are strongly associated with the development and severity of BPD and late PH at 36 weeks (2). They also found that maternal diabetes and invasive mechanical ventilation support at 1 week of age were associated with LRD. Although BPD was predictive of LRD, there were 32 infants (14%) who did not have echocardiographic evidence of early PVD, late PH, or clinical BPD, but did have LRD. The article pursues the "vascular hypothesis," which states that pulmonary vascular disturbances can contribute to later pulmonary dysfunction in former preterm infants. These data show that early identification of PVD, independent of later development of BPD, may contribute to the pathobiology of longer-term respiratory morbidity in former preterm infants.

The study is timely, as the ability of a BPD diagnosis to predict the impact of prematurity on respiratory disease beyond the neonatal period has been questioned. Similar to the large, prospective multicenter cohort study from the NIH PROP (Prematurity and Respiratory Outcomes Program) (12), these data identify those preterm infants at risk of developing late respiratory morbidity in the first week of life. Although prediction of late morbidity by perinatal risk factors and BPD alone in the PROP cohort exceeded that of the current study, it is likely that both perinatal and postnatal factors affect the airspaces and the pulmonary vasculature, driving the clinical trajectories of children born prematurely. The identification of high-risk infants earlier in their course may provide a critical window for applying established or emerging therapies to prevent progressive PVD and PH and to improve late respiratory morbidities (12).

Significant challenges exist in the noninvasive assessment of pulmonary hemodynamics and thereby in the identification of key adaptive mechanistic underpinnings of PVD in premature infants (9). Traditional echocardiographic markers of PH have relied on a combination of qualitative assessments (interventricular septal wall motion and right ventricular [RV] morphological changes) and quantitative estimates based on the tricuspid regurgitant jet velocity. Echocardiographic evidence of PVD often precedes the onset of overt clinical signs, symptoms, and detection of PH. In the pulmonary circulation, the key components of RV afterload, resistance and compliance, evolve together, but in opposite directions in both health and disease (13). In early PVD, a small increase in PVR is accompanied by a significant reduction in vascular compliance, an initial response that may not result in an immediate change in pulmonary arterial pressure, limiting the applicability of many of the current screening modalities that only rely on detecting an increase in pressure. With more advanced stages of PVD (i.e., PH), vascular stiffness will reach its maximum limits, and any further increase in PVR is not associated with further reduction in compliance. The recognition of alterations in septal

Originally Published in Press as DOI: 10.1164/rccm.201810-1983ED on November 5, 2018