definition; *2*) the definition of sepsis will likely continue to evolve, and we developed the temperature trajectory subphenotypes to be generalizable to past and future definitions; and *3*) temperature trajectories derived only from patients with organ dysfunction on presentation would exclude patients with infection who later developed sepsis during hospitalization; because the development of organ dysfunction due to infection is likely in part related to the immune response, we did not want to exclude these patients from our analysis.

On the suggestion of Dr. Maitra and Dr. Bhattacharjee, we tested the association between temperature trajectory membership and mortality adjusting for the Sequential Organ Failure Assessment (SOFA) score instead of the quick SOFA score. In logistic regression, when we controlled for age, comorbidities, SOFA, and time to antibiotics, membership in the "hyperthermic, fast resolvers" group remained associated with decreased mortality risk (odds ratio, 0.55; 95% confidence interval, 0.42–0.72; $P < 0.001$) compared with the "normothermic" group. Membership in the "hypothermic" group was associated with increased mortality risk (odds ratio, 1.56, 95% confidence interval, 1.30–1.88; $P < 0.001$). These results are similar to those we obtained in the primary analyses presented in our paper.

Although the metric used to determine the accuracy of sepsis definitions is often risk of mortality, definitions developed based on that outcome may not capture the heterogeneity of the sepsis syndrome (2, 3). Developing a trajectory model based on body temperature (a biologically relevant clinical measurement) allowed us to establish subphenotypes that were disentangled from but still predictive of the outcome. Further studies are required to establish the precise biological significance of the temperature trajectory subphenotypes. ■

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

Sivasubramanium V. Bhavani, M.D.*
University of Chicago
Chicago, Illinois

Philip A. Verhoef, M.D., Ph.D.
Kaiser Permanente
Honolulu, Hawaii

Matthew M. Churpek, M.D., M.P.H., Ph.D.
University of Wisconsin
Madison, Wisconsin

ORCID IDs: 0000-0002-9640-6720 (S.V.B.); 0000-0002-1502-5468 (P.A.V.).

*Corresponding author (e-mail: sivasubramanium.bhavani@uchospitals.edu).

References

1. Bhavani SV, Carey KA, Gilbert ER, Afshar M, Verhoef PA, Churpek MM. Identifying novel sepsis subphenotypes using temperature trajectories. *Am J Respir Crit Care Med* 2019;200:327–335.
2. Churpek MM, Snyder A, Sokol S, Pettit NN, Edelson DP. Investigating the impact of different suspicion of infection criteria on the accuracy of quick sepsis-related organ failure assessment, systemic inflammatory response syndrome, and early warning scores. *Crit Care Med* 2017; 45:1805–1812.
3. McLymont N, Glover GW. Scoring systems for the characterization of sepsis and associated outcomes. *Ann Transl Med* 2016;4:527.

Role of Transbronchial Cryobiopsy in Interstitial Lung Diseases: An Ongoing Tale

To the Editor:

We read with great interest the study by Romagnoli and colleagues addressing the histological diagnosis of interstitial lung diseases (ILD) (1). Although transbronchial lung cryobiopsy (TBLC) has been suggested as an initial procedure to obtain tissue from patients with ILD, there is much debate regarding its diagnostic yield, and it is not supported by current guidelines (2). This is the first study to prospectively compare the results of TBLC with the "gold standard" surgical lung biopsy (SLB) in the same patients, and as such, it has been highly anticipated.

However, we have some concerns regarding the interpretation of the results, which led the researchers to conclude that "there is no role for TBLC in the vast majority of patients where histopathology is required for definitive diagnosis of diffuse ILD" (1). As implied by the authors, a distinction should be made between the pathological diagnosis *per se* and the "final diagnosis" as decided by a multidisciplinary assessment (MDA).

In fact, previous studies that compared the results of SLB with final diagnoses made in explanted lungs showed a poor correlation with a pathological diagnosis of usual interstitial pneumonia (3, 4).

Moreover, previously reported interobserver agreement levels for a histopathological diagnosis of ILD by SLB were not high, even in centers with extensive experience (5). The degree of interobserver agreement (i.e., concordance) between the blinded pathological review and the routine pathological reports from SLB are not reported in the current manuscript, although they are mentioned in the Methods section (1). Therefore, we used the data from Tables 2 and E1 in Reference 1 to calculate it. We found an agreement level of 57.1%, with a κ-concordance coefficient of only 0.44 (0.215–0.66). Arguably, this relatively low level of agreement between two pathologists may make one question how "golden" the SLB gold standard is.

Therefore, given that the interobserver agreement level is only 57.1%, it is no wonder that the agreement between SLB and TBLC is also poor, as the article's title suggests. Furthermore, the authors' statement that "patients who are able to undergo SLB should be recommended to do so" is not entirely supported by their data and does not take into account the morbidity and mortality risks of the procedure.

Originally Published in Press as DOI: 10.1164/rccm.201908-1559LE on September 19, 2019

The level of agreement between SLB and MDA was 62% (95% confidence interval, 38–82%), which is somewhat low for a gold standard. Although this is slightly higher than the level of agreement between TBLC and MDA (48%), it is not significantly different (95% confidence interval, 26–70%). Besides overlapping confidence intervals, it is possible that a bias shifted the scale toward SLB, as SLB and TBLC were discussed simultaneously in one MDA meeting. This might be problematic, because clinicians and pathologists are more familiar with SLB than with TBLC. Furthermore, the SLB samples were on average 5–10 times larger than the TBLC samples, as would be expected. Taken together, these observations suggest that the SLB diagnosis probably influenced the MDA significantly more than the TBLC diagnosis. Therefore, the better concordance between the blinded pathological diagnosis of SLB and the MDA seems inherent to the process itself.

A better assessment would be to conduct two separate MDA discussions, one using TBLC and the other using SLB samples, and calculate the concordance between them or between each blinded assessment and its corresponding MDA. In addition, it would have been prudent to subject the samples to blinded assessments by at least two pathologists rather than one.

Thus, we believe that rejecting the role of TBLC in the assessment of ILD is premature. We agree that further prospective studies to assess the role of TBLC in the diagnostic evaluation of ILD are warranted. The ongoing prospective COLDICE (Cryobiopsy versus Open Lung Biopsy in the Diagnosis of Interstitial Lung Disease) study (6) is designed to address many of the aforementioned issues, and is expected to provide more conclusive evidence for the role of TBLC in ILD diagnosis. ■

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

Ori Wand, M.D.*
Meir Medical Center
Kfar Saba, Israel
and
Tel Aviv University
Tel Aviv, Israel

Avraham Unterman, M.D.
Tel Aviv University
Tel Aviv, Israel
and
Yale University
New Haven, Connecticut

Gali Epstein Shochet, Ph.D.
David Shitrit, M.D.
Meir Medical Center
Kfar Saba, Israel
and
Tel Aviv University
Tel Aviv, Israel

ORCID IDs: 0000-0002-7702-2967 (O.W.); 0000-0003-0965-3326 (A.U.); 0000-0002-3417-9171 (G.E.S.).

*Corresponding author (e-mail: ori.wand@clalit.org.il).

References

1. Romagnoli M, Colby TV, Berthet JP, Gamez AS, Mallet JP, Serre I, *et al*. Poor concordance between sequential transbronchial lung cryobiopsy and surgical lung biopsy in the diagnosis of diffuse interstitial lung diseases. *Am J Respir Crit Care Med* 2019;199:1249–1256.
2. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, *et al*.; American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018;198: e44–e68.
3. Katzenstein AL, Zisman DA, Litzky LA, Nguyen BT, Kotloff RM. Usual interstitial pneumonia: histologic study of biopsy and explant specimens. *Am J Surg Pathol* 2002;26: 1567–1577.
4. Rabeyrin M, Thivolet F, Ferretti GR, Chalabreysse L, Jankowski A, Cottin V, *et al*. Usual interstitial pneumonia end-stage features from explants with radiologic and pathological correlations. *Ann Diagn Pathol* 2015;19:269–276.
5. Nicholson AG, Addis BJ, Bharucha H, Clelland CA, Corrin B, Gibbs AR, *et al*. Inter-observer variation between pathologists in diffuse parenchymal lung disease. *Thorax* 2004;59:500–505.
6. Troy LK, Grainge C, Corte T, Williamson JP, Vallely MP, Cooper W, *et al*.; COLDICE Investigator Team. Cryobiopsy versus open lung biopsy in the diagnosis of interstitial lung disease (COLDICE): protocol of a multicentre study. *BMJ Open Respir Res* 2019;6:e000443.

Reply to Wand *et al.*

From the Authors:

We read with interest the letter to the editor from Wand and colleagues, who highlighted some concerns about the findings in our recent article, which showed a poor concordance between lung histology from sequential transbronchial lung cryobiopsies (TBLC) and surgical lung biopsies (SLB) obtained prospectively from the same patient during the same surgical procedure.

We obviously agree with the authors regarding the critical importance of multidisciplinary assessments (MDAs) in the diagnostic evaluation of interstitial lung diseases (ILDs) (1, 2), despite the reported low agreement among MDAs for ILDs that are not idiopathic pulmonary fibrosis (3). However, the role of MDAs was not the main focus of our study. Our goal was to assess the concordance of pathological diagnoses *per se* obtained by two different procedures (TBLC and SLB) performed in the same patient, blinded to any clinical information—something that has never been done before. We do believe that our blinded histology approach was somewhat artificial, and we agree that it was outside the routine clinical workflow, as clearly stated in our article (1). However, we

Originally Published in Press as DOI: 10.1164/rccm.201909-1736LE on September 19, 2019