number of important implications. First, from a clinical perspective, early loss of small airways helps to explain why patients with IPF usually have significant loss of $D_{L_{CO}}$ even when presenting with minor symptoms. This, in turn, reiterates the need for clinicians to consider early therapy given that such loss is likely irreversible. Second, their data provide potential insights into the role played by MUC5B in the pathogenesis of IPF. Third, the observation that loss of small airways is a feature of a range of respiratory diseases, including chronic obstructive pulmonary disease, cystic fibrosis, and IPF, highlights the importance of ensuring good lung health, especially during lung development. Finally, knowing that small airway loss is important in the development of IPF provides an opportunity for new therapeutic strategies.

Although the small airways of the lung can be considered the quiet zone, they should not remain a forgotten zone. Knowledge that loss of these important terminal airways occurs early in the evolution of IPF should serve as a wake-up call for the respiratory community to better understand the determinants of optimal development of small airways and to identify what can be done to prevent their premature loss in chronic respiratory disease. ■

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Check for updates

Breathing Hope into Directed Therapy for Pulmonary Infections

Empiric therapy for respiratory infections, including pneumonia and exacerbations of chronic obstructive pulmonary disease (COPD), has remained the norm despite decades of promise that new diagnostic techniques and platforms would deliver clinicians accurate, timely, and affordable information on the pathogen(s). Although microbiological tests have been part of our standard of care for patients at risk of unusual or antibiotic-resistant pathogens, they have had little to no impact on initial therapy. As each successive pneumonia guideline has

pointed out (1, 2), there is no evidence that traditional diagnostic offerings from the laboratory have any meaningful impact on patient outcomes or clinician behavior in usual settings. Equally, in the setting of acute exacerbations of COPD, it is well recognized that although viral pathogens are extremely frequent, there is substantial overuse of antibiotics owing to clinical uncertainty over the pathogen(s). Although recently some small gains had been made, such as the use of rapid-diagnostic platforms to screen for methicillin-resistant *Staphylococcus aureus* (3), the sense of promise molecular methods engendered in the 1990s still remained to be realized.

Then, along came coronavirus disease (COVID-19) and changed the world's perspective on the importance of having the ability to rapidly determine the pathogen(s) in play. In the last 18 months, we have seen a massive uplift in the capability of "ordinary" hospitals to rapidly process respiratory samples, driven by clinical need and

loosening of the normally tight fiscal controls over new technology. A host of platforms are now in widespread use, and when COVID-19 finally retreats into being just one of the usual pathogens we need to deal with each winter, there is likely to be an explosion of knowledge arising from this vast increase in availability and use of the latest generation of diagnostic tools.

However, if we are to truly drop concepts like "community-acquired pneumonia" or "acute exacerbation of COPD" and move to pathogen-specific therapeutic approaches, a number of hurdles need to be crossed. Although the designs of many of the new platforms are amenable to point-of-care use, in most settings, they remain based in traditional laboratories, adding complexity and time to a time-critical decision process. Breaking down traditional fiefdoms and developing greater trust in their use as true point of care devices will take time. The challenge of altering clinician behavior, particularly in using diagnostic data to reduce the use of broad-spectrum antimicrobials, should not be underestimated, as it has been a struggle to achieve this with conventional microbiological tests (4–7). We will need new trials to tell us what the significance of multiple pathogens being present means: are these sequential or concurrent infections, and does the presence of one or more additional pathogens alter the treatment or prognosis?

Perhaps the biggest barrier, however, remains getting adequate specimens from patients for analysis. Obtaining an adequate sputum specimen is a challenge in somewhere between one-third and one-half of patients with community-acquired pneumonia (7, 8) and even more in nonventilated hospital-acquired pneumonia (9). In acute exacerbations of COPD, obtaining sputum is easier but still not achievable in a significant minority of patients (10). This is a fundamental limitation for molecular techniques. Nasopharyngeal aspirates have their own technical challenges, and, although now well accepted for many viral infections and not harmful, they remain highly questionable for bacterial infections and can be unpleasant. Saliva or oral wash samplings have proven useful in COVID-19 (11) as they have *Pneumocystis* (12), but, again, their utility in bacterial infection is problematic and unlikely to be high. How, then, do we move forward if our current generation platforms are not going to help us in a sizeable proportion of patients with lower respiratory tract infection?

In this issue of the *Journal*, Kamal and colleagues (pp. 1075–1085) show one possible way to progress (13). In their study of infected airway epithelial cell cultures, exhaled breath samples from healthy subjects challenged with rhinovirus and patients with COPD, Kamal and colleagues (13) used use highly sensitive gas-chromatography mass spectrometry to detect volatile organic compounds (VOC) as diagnostic signatures of infection. VOC are expelled in the airways in response to infection. Bacteria release VOC as part of their metabolic process, and many have characteristic signatures (14). In both bacterial and viral infections, VOC are released as part of the inflammatory process from airway epithelial cells (15), and whether these have diagnostic signatures was addressed by Kamal and colleagues (13).

Through screening a variety of VOC, they showed that in tissue culture, rhinovirus infection increased the production of decane, but *Streptococcus pneumonia* and *Haemophilus influenza* did not, suggesting this maybe a useful marker for differentiating viral from bacterial infection. They next demonstrated that infecting healthy volunteers with rhinovirus induced the production of decane and other long-chain alkanes in proportion to other inflammatory responses and to viral load. Finally, in a cohort of 139 patients with

COPD, they assessed VOC in exhaled air while stable and again during exacerbation in the 98 who did so during the period of the study. In viral exacerbations, the long-chain alkane 2,9 methyl undecane was significantly increased and correlated with the severity of exacerbation. In patients with bacterial, mixed viral/bacterial, or no pathogen identified, 2,9 methyl undecane was not elevated, suggesting that it may be a useful marker of pure viral infection and therefore potentially a useful tool for limiting antibiotic use in the setting of lower respiratory tract infections.

Clearly the work by Kamal and colleagues is not yet a point-of-care diagnostic box and has many steps to go before reaching that point. However, the appeal of a diagnostic tool patients simply breath into that can rapidly determine whether an infection is viral or bacterial, and if so, which bacteria, is immensely appealing. Such an "electronic nose" may also have applications well beyond infection, as characteristic VOC signatures have been shown to be present in many systemic disease processes, including a variety of cancers (16). Thanks to COVID-19, enthusiasm to progress such technology is likely to be high, and, hopefully, unlike molecular diagnostic tools, we will not have to wait three decades to see a fully functional product in our hospitals. ∎

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Check for updates

Individualized Treatment Duration in Tuberculosis Treatment
Precision versus Simplicity

In 1991, the World Health Organization (WHO) introduced the Directly Observed Treatment–Short course strategy for global tuberculosis (TB) control (1, 2) This strategy simplified TB diagnosis and standardized TB treatment so that this could be decentralized to peripheral Heath centers in resource-limited settings. Front line workers, who are usually not physicians, ask one simple question ("Have you ever been treated for TB before?"), perform one simple test (Sputum Acid-Fast Bacilli Smear), and then initiate a standardized 6-month regimen. This "one size fits all" approach has been successful from a global public health perspective. WHO has estimated that between 2000 and 2019, 60 million deaths were averted because of the Directly Observed Treatment–Short course strategy (3).

To an observer from outside the TB community, the designation of a 6-month regimen as "short-course therapy" may seem like an oxymoron. Compared with the progress made over the last three decades with shortening treatment of other infectious diseases to as little as one dose, there has been little progress in shortening treatment in TB despite multiple large-scale trials (4–7). If anything, increased rates of failure and/or relapse with 6 months of therapy have been described in patients with various indicators of more extensive disease, suggesting that there is an identifiable subgroup of patients for whom the current 6-month regimen is too short (8–11).

In this issue of the *Journal*, Imperial and colleagues (pp. 1086–1096) analyzed individual patient data from four randomized trials to identify patient clinical characteristics that can accurately predict the duration of TB therapy required for relapse-free cure (12). Using pretreatment (baseline) HIV status, body mass index, Acid-Fast Bacilli sputum smear grade, and chest X-ray, plus 2-month culture results, patients were accurately allocated into three risk groups. The lowest risk group had excellent TB treatment outcomes with only 4 months treatment, whereas those in the moderate risk category had optimal results with 6 months duration. On the other hand, 29% of patients at high risk of treatment failure or relapse appeared to require more than 6 months of therapy. The authors conclude that this risk categorization may be useful for clinical care and for planning further randomized trials. They have also provided a web-based calculator for the determination of risk to help plan clinical trials.

Strengths of this study are that it is based on a sophisticated analysis of carefully collected and complete data from participants in four trials conducted in many different settings and populations. The prediction model was derived from the data in three trials and validated with the data from the fourth as well as validated in a randomly selected sample from all data. The prediction algorithm is simple and based on readily available clinical information, at least in high-income countries. The concept of individualized therapy based on an accurate estimate of need is very attractive. The finding that almost a third of all patients were at high risk of poor outcomes with 6 months of treatment is a sobering reminder of the limitations of the current standardized regimen.

We see some important limitations in the application of these findings in resource-limited settings in which improved TB treatment is most needed. For example, in Benin, the national TB program does not recommend routine performance of chest radiography before or during TB treatment for Smear- or GeneXpert-positive patients. At the moment, patients must pay out of pocket for the X-rays—a substantial financial barrier. Because culture facilities are not available in many parts of the country, sputum cultures are done only if treatment failure is suspected. More importantly, active TB is detected and treatment initiated in peripheral health centers throughout the country by frontline workers following simple algorithms, as recommended by WHO. Hence, the applicability of a more complex treatment algorithm would be limited in Benin and likely in other resource-limited settings without substantial additional training.

How many patients in high-burden settings would be eligible for a shortened 4-month regimen? Based on the findings from the