One Step Closer: Nontuberculous Mycobacterial Pulmonary Disease and Predicted Mortality—The BACES Score

Nontuberculous mycobacterial (NTM) pulmonary disease (PD) has substantially increased in prevalence and awareness over the past several decades (1–3). Robust engagement from patients with NTM PD has further catalyzed and informed efforts for a comprehensive and systematic approach to the further understanding of the natural history, treatment options, and research priorities for NTM PD (4). Recent investigations and developments in NTM PD have additionally spawned a heightened interest worldwide to advance the science and begin to fill unmet needs (5). These efforts have resulted in the first positive large prospective international clinical treatment trial of any NTM PD, first U.S. Food and Drug Administration approval of a medication for refractory *Mycobacterium avium* complex (MAC) PD, and an update of the previous 2007 American Thoracic Society Infectious Disease Society of America NTM diagnosis and treatment of NTM PD guidelines (6, 7).

In this issue of the *Journal*, Kim and colleagues (pp. 230–236) have further expanded an increasing body of literature of predicting outcomes, namely mortality, in patients with NTM PD (8–12). These investigators are highly experienced and well published in mycobacterial PD and based in two national tertiary referral centers in South Korea. They have quite appropriately and sequentially drawn from their large mycobacterial patient cohort database for a derivation cohort of 1,181 patients followed by a validation cohort of 377 patients to develop a scoring system to predict all-cause mortality in patients with NTM PD attributed to the most common NTM PD species in East Asia and North America, including *M. avium*, *M. intracellulare*, *M. abscessus* subsp *abscessus*, *and M. abscessus* subsp *massiliense* (2, 13).

Predictors of mortality in this study of patients with NTM PD were correlated in an additive fashion and included BMI <18.5 kg/m^2, age ≥ 65 years, presence of cavitary lung disease, elevated erythrocyte sedimentation rate (ESR), and male sex (BACES score). Although univariate risk was also associated with sputum acid-fast bacillus smear positivity, this association fell sufficiently in multivariate analysis to not be included as one of the elements of the BACES score. On balance, several strengths are readily apparent from the validated scoring for predicted mortality. The elements of the BACES score are simple, easily obtained, and straightforward for clinical care as well as research trials. Moreover, the performance of the BACES score confirmed in the validation cohort of 377 patients was very strong. These findings will clearly potentially aid clinicians and researchers alike in recommendations to guide best care for patients with NTM PD.

Despite these findings providing one important step forward, several more steps are needed to address unanswered questions, clarify findings, and leverage opportunities brought forward regarding NTM PD. First and foremost, the decision to start or hold treatment for an established diagnosis of NTM PD is complex and requires robust communication between patients and providers guided by a risk–benefit assessment of treatment as well as adjudication of expectations of goals of care (1). Mortality, though representing a distinct and unequivocal end point in itself, comes by definition much too late in the natural history of this disease. More specifically, modeling of factors that predict the development of cavitary lung disease, an elevated ESR, and reduced BMI would add needed early granularity in the natural course of the disease and support the shared decision-making of patient and provider as to whether or not to begin NTM PD treatment with the presupposition of improving patient outcomes.

We are furthermore left with unresolved controversies based on these findings, not the least of which is what proportion of patients with NTM PD included in this study dies with, rather than from, NTM PD. The implication and unanswered question of course is whether intervention(s) for other comorbidities may impact outcomes, including those mentioned by the authors, such as malignancies, concomitant fungal infection (e.g., *Aspergillus*), or chronic heart or liver disease, as well as unmentioned comorbidities, such as bronchiectasis, chronic obstructive pulmonary disease, diabetes mellitus, or others. Clinical signs or symptoms that are free standing or symptoms that are in association with patient-reported outcome measures may be predictive of disease progression to favor the start of treatment in risk–benefit analyses. Short of mortality, these quality-of-life measures vis-à-vis patient-reported outcome instruments as well as assessment of microbiologic and radiographic status hold potential to further inform patients and clinicians. NTM species–specific mortality data in this study did not support the association between NTM species and mortality, which is at odds with previous publications (14, 15). The extent to which there is variation in virulence between specific NTM species and mortality in the BACES model is left unanswered at this point in time.

Interestingly, although the adjusted hazard ratios in this study were relatively similar across the BACES score calculations (perhaps age being slightly higher) and Kaplan-Meier curves of survival probabilities similar across cohorts, it is unclear whether there may be synergistic relationships between specific BACES risk factors. For example, would a young male with NTM PD with cavitary disease and low BMI have a similar predicted outcome as an older female with elevated ESR and low BMI without cavity independent of comorbidities? This type of analysis may assist in the assessment of all-cause mortality for patients with NTM PD in contrast to NTM PD–attributed mortality, with implications on the potential timing to start of treatment and best clinical care.

Specific treatment regimens were not mentioned other than noting adherence to guideline-based therapy. For example, it is unclear whether patients with MAC with cavitary disease all received triple-drug daily MAC mycobacterial therapy (macrolide, rifamycin, and ethambutol) as well as parenteral amikacin and what impact any variation in treatment regimens may have had. Variations in treatment regimens for rapid growers have been equally notorious (16, 17).

On balance, investigators have nicely presented a first step from a large cohort to derive and then validate a robust predictive model of mortality in patients with NTM PD. In the journey for better assessment, diagnosis, and management of NTM PD, the next critical

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steps to be addressed include a further understanding of the natural history of, different host phenotype responses to, species-specific virulence characteristics, optimal treatment strategies, and environmental factors leading to the progression of NTM PD (e.g., innate host immunity, environmental exposure, and impact of other comorbidities). We may, in fact, be at the dawn of a new understanding of a much needed expansion of associated epidemiologic, pathophysiologic, diagnostic, and therapeutic possibilities of NTM PD as a credit to all those involved in the care of NTM PD, including patients, clinicians, and investigators. ■

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National Asthma Education and Prevention Program 2020 Guideline Update: Where Do We Go from Here?

The U.S. National Asthma Education and Prevention Program (NAEPP) oversaw the development of national asthma guidelines nearly 30 years ago (1). Since that time, there have been two major revisions (1997 and 2007) and one interim update (2002). In December 2020, the 2020 Focused Update to the Asthma Management Guidelines was released—the first update to the guidelines in 13 years (2).

The NAEPP 2020 update adheres to standards for trustworthy guidelines promulgated by the U.S. National Academy of Medicine, including a systematic review of the evidence that addresses specific questions, a multidisciplinary panel of experts and representatives of key affected groups, consideration of important patient subgroups and preferences, an explicit and transparent process to minimize bias

All three authors are members of the Expert Panel, and one (J.A.K.) is also a member of GINA. The views expressed in this article are their own and should not be taken as representing the views of the NAEPP Expert Panel nor GINA.

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