HALTing Nontuberculous Mycobacteria in Cystic Fibrosis Centers

Is There Something in the Water?

Since 1990, there have been increasing reports of nontuberculous mycobacteria (NTM) in people with cystic fibrosis (pwCF), raising questions of whether there is person-to-person transmission or environmental acquisition in cystic fibrosis (CF) centers where pwCF receive care (1). The first multisite study that prospectively screened for NTM within U.S. CF centers reported a prevalence of 13% and assessed for molecular similarity of *Mycobacterium avium* complex and *Mycobacterium abscess* isolates between patients with CF within the same centers. Essentially all had molecularly distinct isolates by pulsed field gel electrophoresis and random amplified polymorphic DNA PCR except for two siblings cultured on the same day at the same site and two other patients cultured within 3 days of each other; both pairs had multiple subsequent cultures that were negative (2). More recently, the question of transmission versus acquisition was raised at a Seattle lung transplant center, where an outbreak of *M. abscessus* with devastating consequences was reported. All had isolates that were indistinguishable using similar molecular methods. Detailed epidemiologic investigation showed four of the five patients were seen at the same time in the same clinic and environmental sampling within the clinic did not detect pathogenic NTM, suggesting direct or indirect transmission (3). The first report using whole-genome sequencing (WGS) to evaluate molecular similarity of isolates identified two clusters of nearly identical isolates of *M. abscessus* subspecies (ss) *massiliense* with fewer base pair differences between patients than was seen between isolates from the same individual. All patients within the clusters had multiple possibilities for physical overlap within the center, and extensive environmental sampling did not show a source for acquisition, again suggesting transmission (4). Subsequent single-site and multisite studies reporting dominant circulating clones by WGS and variation in accompanying epidemiological investigations have yielded conflicting conclusions with regard to person-to-person transmission versus environmental acquisition (5–9).

In this issue of the *Journal*, Gross and colleagues (pp. 1064–1074) report a retrospective study, HALT-NTM (Healthcare-associated Links in Transmission of NTM; NCT04024423), that used WGS and a systematic, evidence-based, standardized epidemiologic approach to investigate the potential for transmission versus environmental acquisition at the University of Colorado Adult CF Center (10). The site had a relatively large number of NTM-positive patients with 165 (33%) of 507 having at least one positive culture. However, more than half of them were excluded for having fewer than four positive cultures during the timeframe of the study, inadequate exposure to the healthcare setting, or lack of available isolates for WGS. They used WGS to assess relatedness at the core genome level. To evaluate possible transmission events within the center for patients within a cluster, they adapted a CDC-validated healthcare outbreak investigation form and toolkit, which used date and location data from their electronic medical record. Core genome analysis identified 11 clusters comprising 27 subjects, with 4 of these clusters (2 *M. abscessus* and 2 *M. avium*) having overlapping opportunities for healthcare transmission. They defined social links, which might account for patient–patient exposures outside the healthcare setting, only by electronic medical record identification of siblings, spouses, or housemates with CF. No attempt was made to survey patients directly about outside social contact. One unique aspect of this study was the assessment of the pan (core + accessory) genome of isolate pairs within clusters, noting two *M. abscessus* clusters (without healthcare overlap) and one *M. avium* cluster (with healthcare overlap) that met the more stringent cut-points of 10 or fewer SNPs' difference between isolates within the cluster and 95% or more shared accessory genome. A second unique aspect of this study, geolocalizing patient addresses to corresponding watersheds, identified one of these stringent cut-point *M. abscessus* clusters without healthcare overlap as residing in the same watershed, suggesting the possibility of common environmental source acquisition outside the center. Environmental sampling of biofilms and dust was done in the healthcare setting but showed no mycobacteria with genetic similarity to the respiratory isolates. The authors conclude that because there were no *M. abscessus* clusters that both met the stringent pan genome criteria for similarity and had overlapping healthcare proximity, transmission of *M. abscessus* was unlikely in that healthcare setting with the infection control practices in place at the time. There was, however, one *M. avium* cluster that met both criteria and another *M. avium* cluster with overlap that differed in pan genome sequence by only 11 SNPs, raising the possibility of *M. avium* healthcare transmission for *M. avium*.

Several gaps remain in these studies seeking to clarify how patients with CF are becoming infected with NTM. WGS of isolates is a huge advance over prior molecular techniques in identifying clusters of near identical isolates. However, the fact that there are dominant circulating clones found in disparate parts of the globe makes it hard to implicate person-to-person transmission, either direct or indirect, within a center with any degree of certainty (6, 11). The increased specificity added by the pan genome sequences in this study may help to further clarify the significance of these clones. Further, there have yet to be studies of NTM cough aerosols to determine the infectiousness relative to distance and time as have been done for *Pseudomonas* (12–13). Furthermore, environmental sampling is not standardized and likely not comprehensive nor performed concurrent with patient proximity to the sampling areas. Although it is possible the infecting strains of mycobacteria may survive in biofilms or dust over prolonged periods, not finding identical strains in environmental sources does not necessarily

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exclude the possibility of healthcare-associated environmental acquisition. The association of a *M. abscessus* cluster meeting this study's stringent pan genome criteria with residence within the same watershed is of interest, but *M. abscessus* has been difficult to culture from environmental sources, and no home-based environmental sampling was done in this study. Because pwCF spend more time in the home and community than in the healthcare setting, environmental acquisition outside the healthcare setting may be a more likely source of exposure. Studies seeking to identify individual risk factors for infection have not found specific behaviors associated with increased risk (14). Rather, water quality and other environmental factors seem to be a stronger predictor of risk than individual behaviors (15). Future environmental studies with increased water sampling in high- and low-risk areas may, in parallel, increase our understanding of environmental acquisition (16).

This study does make a significant contribution to the building literature seeking to address NTM transmission and acquisition. One of the most promising aspects is its planned extrapolation to other CF centers, which is already underway using a standardized study design (17). With increasing numbers of same-site clusters being evaluated in a similar fashion at multiple geographically dispersed centers with variations in infection control practices, additional data may help to clarify the validity of the findings in this study. ■

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