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JOURNAL CLUB

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ARTICLE

"Time to Positivity Culture Detection Predicts *Mycobacterium avium* Pulmonary Disease Severity and Treatment Initiation". Edwards Brett D., et al. *Ann Am Thorac Soc*. 2022 Jun;19(6):925-932. DOI: 10.1513/AnnalsATS.202107-765OC; PMID: 34851813

CLINICAL QUESTION

Biomarkers are needed to guide the decision to initiate therapy in *Mycobacterium avium* pulmonary disease. Does time to positive sputum culture detection (TTP) offer potential prognostic or monitoring value?

SUMMARY

Background:

Nontuberculous mycobacteria (NTM) are ubiquitous in the environment and the prevalence of NTM pulmonary disease is increasing in many parts of the world. *Mycobacterium avium* is one of the most common organisms found in patients infected with *M. avium* complex (MAC). Studies have shown that approximately 60% of patients with pulmonary MAC have progression of symptoms or radiographic findings that warrant the initiation of therapy. The decision to initiate treatment is challenging and typically supported by a combination of clinical, microbiologic and radiographic features. Clinicians would benefit from additional tools to assist in the decision-making regarding treatment initiation. Sputum smear and culture is a routine component of the diagnosis and monitoring of patients with NTM pulmonary disease. Liquid culture methods allow for reporting of time to positive culture. It is hypothesized that a heavier mycobacterial burden will lead to earlier detection in the indicator tube, therefore it will be inversely associated with disease burden. The authors hypothesize that TTP will offer a new tool for diagnostic clarification, prognostication and treatment monitoring.

Methods:

This is a retrospective cohort study of patients seen at the Toronto Western Hospital NTM clinic between January 1, 2015 through December 21, 2019. Patients had to meet the microbiologic criteria for NTM pulmonary disease which includes two positive sputa for *M. avium*. There was no time limit between the two sputa and only the index isolate was required to meet criteria for study inclusion. If multiple sputa met criteria for the index, only the earliest sample was chosen. Patients were not actively receiving treatment and could not have been on MAC treatment within the last six months. Finally, patients had computed tomographic (CT) imaging of the chest within six months of their index sputum result.

The primary objective was to assess if TTP correlated with the presence of NTM pulmonary disease, severity of *M. avium* pulmonary disease (MAC-PD) and clinical trajectory. TTP was defined as the date of the laboratory receipt of the sputum to the date of culture confirmation. Patients were classified as having disease if they had concomitant clinical and radiographic criteria as outlined in the international NTM guidelines. TTP was tested for association with markers of infection severity (MAC-PD, bronchiectasis, cavitary disease, treatment initiation by 3 and 6 months, and AFB smear) and treatment response using Mann-Whitney U, Spearman's correlation coefficient and Wilcoxon signed rank tests. Culture conversion was defined as three consecutive negative sputum specimens separated by at least 4 weeks while on antimycobacterial therapy. The authors explored a predictive threshold TTP that could distinguish between *M. avium* disease vs. colonization as well as subsequent treatment initiation.

Results:
541 patients were identified on the initial screen for inclusion. 416 were excluded due to the following reasons: on treatment (130), unavailable microbiology results (117), lack of CT scan within 6 months (98), single *M. avium* isolate (32), no TTP data or mixed mycobacterial growth (36), or unavailable chart (3). 125 patients met the inclusion criteria for evaluation. The median (IQR) index TTP was 12 (10-15, range 6-44) days. The overall disease severity of the cohort was mild to moderate with the majority of patients having negative sputum smear (62.4%) and less than 10% had a cavity of over 20mm. 65% met criteria for NTM pulmonary disease. 27% initiated treatment within 6 months of the index sputum and overall, 42.4% of patients initiated treatment. TTP was associated with several markers of disease severity including smear status ($p < 0.001$), presence of NTM disease ($p=0.03$), and treatment initiation within 3 months ($p= 0.001$) and 6 months ($p=0.03$).

A TTP of 10 days or less demonstrated a favorable partition of the cohort and association with all parameters tested. After 3 and 6 months of treatment the median (IQR) change in TTP was 8 (1 undefined; $p<0.001$) and 7 (0 undefined; $p=0.001$) days respectively. The presence of a cavity (12, 9.6%) was not associated with a statistically shorter TTP. Survival analysis did not associate TTP with time to treatment initiation (unadjusted or adjusted). The presence of NTM disease and a cavity was the only hazard significantly associated with time to treatment initiation. ($P<0.001$)

GROUP OPINION

NTM pulmonary disease is lacking in biomarkers to aid clinicians in the management of this diverse disease state. Smear positivity is associated with severity of disease but the majority of patients have a negative smear therefore it lacks sensitivity. TTP in tuberculosis correlated inversely with smear status and colony concentration supporting the hypothesis that a shorter TTP is associated with a higher bacterial burden. In tuberculosis TTP may be more sensitive to treatment response than smear status. This study of *M. avium* infection found a numerically higher proportion of patients increase their TTP compared with reducing their smear grade after early treatment therefore it appears to afford greater sensitivity.

Semiquantitative culture counting has been proposed to serve as a surrogate to qualify the clinical significance of positive cultures as well as treatment response, but unfortunately this method is labor intensive and not a standard method in most laboratories.

In this study of patients with *Mycobacterium avium* pulmonary disease, time to positivity was associated with bacterial burden, disease severity and treatment response. Additionally, TTP of 10 days or less is predictive of disease severity and may have the potential to be used as a threshold for the initiation of treatment.

This study was limited by the retrospective design. Additionally, only 42% of the included patients underwent treatment sometime after their index isolate and only 55% and 60% had sputum available for analysis at the specified 3- and 6-months intervals respectively. It is unclear what constitutes a significant change in TTP and whether TTP changes early in treatment are associated with durable culture conversion which is the ultimate goal of treatment. However, as a readily available biomarker, further research ideally with a larger cohort and a prospective design of TTP is warranted.

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