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Letter to the Editor

Prediction of 1-year treatment outcome using early sputum culture conversion status in *Mycobacterium abscessus* pulmonary disease

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Sir,

According to the NTM-NET consensus statement, a treatment period of ≥12 months is a prerequisite condition to evaluate the treatment outcome of nontuberculous mycobacterial pulmonary disease (PD), whether the outcome is treatment failure or not [1]. However, 12 months appears to be too long, especially for patients with *Mycobacterium abscessus* subsp. *abscessus* (*M. abscessus*) PD. This is because (i) *M. abscessus* PD requires prolonged therapy including intravenous (i.v.) antibiotics, (ii) adverse events to the parenteral agent frequently develop during treatment and (iii) the treatment success rate is only 30–40% even with treatment for ≥12 months [2,3]. Unnecessary long-term treatment in these patients could be avoided by the presence of a clinical marker that can predict the treatment outcome early during the treatment course. Therefore, this study aimed to investigate whether serial sputum conversion status after treatment initiation could be used as an early microbiological predictor to determine 1-year treatment outcome in *M. abscessus* PD.

Medical records of patients with *M. abscessus* PD treated with i.v. amikacin for ≥8 weeks and i.v. β-lactams for ≥2 weeks at three tertiary referral centres in Seoul, South Korea, were retrospectively collected from 2005–2019. Treatment modality was not predefined but was determined by attending physicians at each centre. Patients were requested to submit the expectorated sputum sample with at least a 1-month interval after treatment initiation. Culture conversion and microbiological cure at 1 year after treatment initiation was determined according to the NTM-NET consensus statement [1]. The study protocol was approved by the Institutional Review Board of each centre, including the Asan Medical Center.

A total of 57 patients were included in the analysis after excluding those whose *M. abscessus* isolate was resistant to clarithromycin [minimum inhibitory concentration (MIC) ≥8 μg/mL at Day 3 of incubation]. The mean patient age was 58.6 years and 68.4% were female. The mean body mass index (BMI) was 20.3 kg/m^2. Sputum acid-fast bacillus smear positivity was observed in 71.9% of patients, and 45.6% of patients showed cavitary lesions. The presence of inducible resistance (IR) to clarithromycin was detected in 73.7% (42/57) of *M. abscessus* isolates. The median duration of i.v. amikacin and β-lactam administration was 26.9 weeks and 8.3 weeks, respectively. Among the oral antibiotics administered, azithromycin was prescribed in 86.0% and clarithromycin in 14.0%. Overall, the microbiological cure rate was 31.6% (18/57).

Table 1
Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and concordance (κ) of sputum culture conversion status in predicting the microbiological cure of *Mycobacterium abscessus* pulmonary disease at 1 year on a monthly basis according to the presence of inducible resistance (IR) to clarithromycin

Months since treatment initiation	Sensitivity	Specificity	PPV	NPV	κ
M. abscessus isolates with IR (n = 42)					
1	0.18	0.94	0.50	0.76	0.15
2	0.45	0.84	0.50	0.81	0.30
3	0.64	0.84	0.58	0.87	0.46
4	0.73	0.87	0.67	0.90	0.58
5	0.73	0.87	0.67	0.90	0.58
6	0.73	0.90	0.73	0.90	0.63
7	0.91	0.90	0.77	0.97	0.77
8	0.91	0.90	0.77	0.97	0.77
9	0.91	0.94	0.83	0.97	0.82
10	0.91	0.94	0.83	0.97	0.82
11	0.82	0.97	0.90	0.94	0.81
M. abscessus isolates without IR (n = 15)					
1	0.57	1.00	1.00	0.73	0.59
2	0.71	1.00	1.00	0.80	0.73
3	0.86	1.00	1.00	0.89	0.87
4	1.00	0.88	0.88	1.00	0.87
5	1.00	0.88	0.88	1.00	0.87
6	1.00	1.00	1.00	1.00	1.00
7	1.00	1.00	1.00	1.00	1.00
8	1.00	1.00	1.00	1.00	1.00
9	1.00	1.00	1.00	1.00	1.00
10	1.00	1.00	1.00	1.00	1.00
11	1.00	1.00	1.00	1.00	1.00

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The relationship between monthly sputum culture conversion status and the treatment outcome at 1 year was analysed. Table 1 shows the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and concordance of monthly sputum culture conversion status in predicting microbiological cure at 1 year. The predictive power of culture conversion status tended to increase in the first 4 months and levelled thereafter.

The NPV of sputum culture conversion at the fourth month of treatment was 90% in patients with isolates with IR. This means that the probability of failure to achieve microbiological cure at 12 months is 90% if the sputum culture positivity persists during the first 4 months from treatment initiation. In addition, its PPV, sensitivity, specificity and overall concordance were 67%, 73%, 87% and 58%, respectively. A PPV of 67% at 4-month sputum conversion means that the likelihood of achievement of microbiological cure at 1 year would be 67% if sputum conversion is achieved in the fourth month of treatment.

Moreover, the NPV of sputum culture conversion at the fourth month of treatment was 100% in patients with isolates without IR, and its PPV, sensitivity, specificity and overall concordance were 88%, 100%, 88% and 87%, respectively. This means that persistent sputum positivity at 4 months indicates the possibility of failure to achieve microbiological cure at 12 months with 100% chance, while the chance of microbiological cure can be estimated as 88% if culture conversion is observed at 4 months after treatment initiation.

The findings of the present study are in line with a previous study revealing that early semiquantitative sputum culture results can predict long-term sputum conversion in *Mycobacterium avium* complex PD [4]. In the study subjects, 4-month conversion status appears to be the best predictor among the monthly sputum within 12 months considering that: (i) the predictive power of the sputum status after 4 months did not appear to be significantly different compared with that of 4 months; (ii) 4 months is an adequate time for the attending physicians to obtain the results of the initial 3 months of sputum culture results; and (iii) it is the early period that corresponds to one-third of the 12-month treatment period.

Therefore, we suggest that sputum culture conversion status at 4 months after treatment initiation could serve as a microbiological indicator of 1-year treatment outcome in patients with *M. abscessus* PD.

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Declaration of Competing Interest

None declared.

Ethical approval

The study protocol was approved by the Institutional Review Board of each centre, including the Asan Medical Center [IRB No.: 2020-1515].

References

[1] van Ingen J, Aksamit T, Andrejak C, Bottger EC, Cambau E, Daley CL, et al. NTM-NET. Treatment outcome definitions in nontuberculous mycobacterial pulmonary disease: an NTM-NET consensus statement. Eur Respir J 2018;51:1800170.

[2] Kwak N, Dalcolmo MP, Daley CL, Eather G, Gayoso R, Hasegawa N, et al. *Mycobacterium abscessus* pulmonary disease: individual patient data meta-analysis. Eur Respir J 2019;54:1801991.

[3] Diel R, Ringshausen F, Richter E, Welker L, Schmitz J, Nienhaus A. Microbiological and clinical outcomes of treating non-*Mycobacterium avium* complex nontuberculous mycobacterial pulmonary disease: a systematic review and meta–analysis. Chest 2017;152:120–42.

[4] Griffith DE, Adjemian J, Brown-Elliott BA, Philley JV, Prevots DR, Gaston C, et al. Semiquantitative culture analysis during therapy for *Mycobacterium avium* complex lung disease. Am J Respir Crit Care Med 2015;192:754–60.

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