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Original Article

Screening, epidemic trends and drug sensitivity analysis of nontuberculous mycobacteria in a local area of China

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Abstract: Objective: To analyze the isolation rate, prevalence trends, species distribution, and drug sensitivity of non-tuberculous mycobacteria (NTM) in Anhui Province, providing a reference for diagnosis and treatment strategies. Methods: Specimens from suspected mycobacterial infection patients at Anhui Chest Hospital (including outpatients and inpatients) from January 2021 to December 2023 were cultured. Identified NTM strains were analyzed for species distribution and drug sensitivity. Results: Of 10,519 mycobacteria strains cultured, 1,589 were NTM (15.11%). The top four species were Mycobacterium intracellulare (75.36%), Mycobacterium abscessus (11.78%), Mycobacterium kansasii (7.09%), and Mycobacterium avium (2.85%). NTM strains showed high sensitivity to amikacin and clarithromycin (≥90%) and significant sensitivity to rifabutin, moxifloxacin, and rifampicin (89.03%-79.61%). They exhibited high resistance to imipenem/cilastatin, sulfamethoxazole, minocycline, and doxycycline (≥95%). Conclusion: NTM isolation rates in Anhui have remained stable, with the predominant species being M. intracellulare, M. kansasii, M. abscessus, and M. avium. NTM strains are highly sensitive to amikacin, clarithromycin, rifabutin, moxifloxacin, and rifampicin. These findings can guide diagnosis, treatment strategies, and drug selection for NTM disease in Anhui Province.

Keywords: Non-tuberculous mycobacteria, species distribution, epidemiology, drug sensitivity

Introduction

Non-tuberculous mycobacteria (NTM) refers to a large group of mycobacteria other than the Mycobacterium tuberculosis complex (MTBC) and Mycobacterium leprae. NTM are widely present in the natural environment, such as soil, water, dust, fish, livestock, and poultry. Although NTMs have only been recognized for about 60 years, nearly 200 species and 14 subspecies have been identified so far. Most of these are commensal, with only a small number pathogenic to humans [1-3]. NTM disease refers to infections caused by NTMs that lead to damage in tissues or organs [1-3]. NTM disease closely resembles tuberculosis in clinical presentation, bacterial morphology, pathologic features, and imaging findings. Without timely bacterial identification, it can be easily mistaken for tuberculosis, leading to treatment failures [4-7]. Studies have shown that the incidence and prevalence of pulmonary diseases caused by NTM infections have increased significantly in regions such as North America, Europe, and East Asia [8-11], drawing growing attention to NTM. Currently, there is a lack of reliable epidemiological monitoring information in China. This retrospective study collected specimens such as sputum, bronchoalveolar lavage fluid, body fluids (blood, cerebrospinal fluid, pleural effusion, pericardial effusion, and ascites), and pus from suspected mycobacterial infection patients who visited Anhui Chest Hospital (including both outpatients and inpatients) from January 2021 to December 2023. These specimens were cultured for mycobacteria, and the strains preliminarily identified as NTM were further analyzed for prevalence trends, species identification, in vitro drug susceptibility testing (DST), and sensitivity analysis. These data may help provide a preliminary understanding of the current state of NTM disease in Anhui, serving as a reference for formulating and adjusting NTM disease diagnosis and

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treatment strategies, and providing important guidance for drug selection in NTM treatment.

Materials and methods

Study design

Patients admitted to or visiting the Anhui Chest Hospital for inpatient or outpatient care from January 2021 to December 2023 were included in the study. Specimens from suspected mycobacterial infections such as sputum, bronchoalveolar lavage fluid, pleural and peritoneal fluids, cerebrospinal fluid, and pus were cultured for mycobacteria. The isolated NTM strains underwent species identification, trend analysis of NTM prevalence, and distribution characteristics analysis in the region. Additionally, during the same period, drug sensitivity test reports of NTM from Anhui Chest Hospital were extracted for drug sensitivity analysis. This study was approved by the Ethics Committee of Anhui Chest Hospital (Approval No. K2021-007).

Mycobacteria culture and NTM species identification

(1) Samples from suspected mycobacterial infections (sputum, bronchial lavage fluid, pleural and peritoneal fluids, cerebrospinal fluid, pus, etc.) were collected, processed and cultured using the BACTEC MGIT 960 liquid culture method. Positive cultures were initially identified using an early secretory antigen target (MPB64) and a para-nitrobenzoic acid (PNB) selective culture medium. Strains with growth on PNB selective medium or negative results for MPB64 antigen were preliminarily identified as NTM (**Figure 1**).

(2) Further species identification was performed using molecular biology techniques. Using the 16S rRNA coding gene and the heat shock protein 65 (hsp65) coding gene method, the 16S rRNA coding gene and the heat shock protein 65 (hsp65) coding gene sequencing sequences were analyzed for species identification. The gene sequences were submitted to BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi) for homology analysis to determine the species level.

In vitro drug susceptibility testing (DST) of NTM

According to the Clinical and Laboratory Standards Institute (CLSI) guidelines [12, 13], in vitro drug susceptibility testing of NTM was performed using the broth microdilution method. The samples were tested against 15 antimicrobial drugs, including clarithromycin (0.5-64 μg/mL), azithromycin (1-32 μg/mL), amikacin (1-64 μg/mL), rifampicin (1-16 μg/mL), rifabutin (0.5-32 μg/mL), cefoxitin (4-160 μg/mL), ethambutol (2.5-20 μg/mL), moxifloxacin (0.125-16 μg/mL), linezolid (0.5-32 μg/mL), tobramycin (0.5-64 μg/mL), doxycycline (0.5-128 μg/mL), minocycline (0.5-128 μg/mL), gatifloxacin (0.06-8 μg/mL), sulfamethoxazole (8-256 μg/mL), and imipenem/cilastatin (0.5-64 μg/mL) using a microplate and a microplate microbial sensitivity testing instrument (YK-909, Zhuhai Yinke Medical Engineering Co., Ltd.). The results were read according to the instructions of the NTM DST microplate kit (Zhuhai Yinke Medical Engineering Co., Ltd.).

Data collection

All data were collected from the electronic medical record system (Wenning LIS 5.5.0.10). Patient demographic and clinical data were collected, including age, gender, mycobacterial culture results, and DST results.

Statistical analysis

Data were analyzed using SPSS 24.0 software. The average age was expressed as mean ± standard deviation, and categorical variables were expressed as case numbers and percentages. Chi-square tests were used for group comparisons, and differences were considered significant at $P<0.05$.

Results

Demographic data

A total of 1,589 NTM strains were isolated from 1/1/2021 to 12/31/2023. Among the 1,588 patients with NTM infections, the minimum age was 15 years, and the maximum age was 90 years, with an average age of 61.89(±14.9) years. Patients aged 60 years and above accounted for the highest proportion (58.82%, 934/1,588). There were 892 male patients and 696 female patients, resulting in a male-to-female ratio of 1.28:1 (more males than females).

NTM isolation rate and species distribution

From January 1, 2021 to December 31, 2023, a total of 10,519 mycobacteria strains were

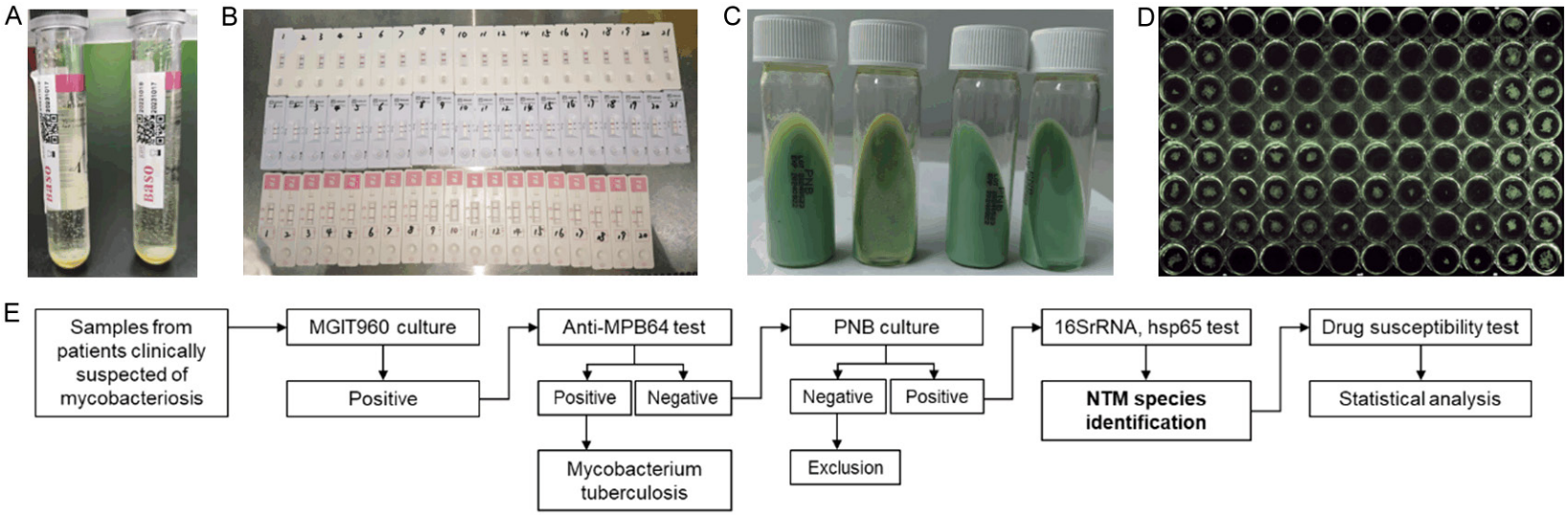

Figure 1. Culture and identification process of NTM. A. MGIT960 liquid culture detection, specimens positive for mycobacteria; B. Representative image of MPB64 antigen detection results; C. PNB culture experiment, with colony growth on the left indicating positivity; D. Drug sensitivity test; E. Flow chart of non-tuberculous mycobacteria culture identification. NTM, non-tuberculous mycobacteria; PNB, para-nitrobenzoic acid.

Table 1. NTM isolation rate

Year	Cultured Mycobacteria	MTBC	NTM	NTM Isolation Rate
2021	3,801	3,256	547	14.39%
2022	3,337	2,821	521	15.61%
2023	3,381	2,861	521	15.41%
Total	10,519	8,938	1,589	15.11%

NTM, non-tuberculous mycobacteria.

Table 2. Proportions of 1,579 single NTM strains

Species	Number	Proportion
Mycobacterium intracellulare	1,190	75.36%
Mycobacterium abscessus	186	11.78%
Mycobacterium kansasii	112	7.09%
Mycobacterium avium	45	2.85%
Mycobacterium gordonae	12	0.76%
Mycobacterium fortuitum	9	0.57%
Mycobacterium lentiflavium sp.nov	7	0.44%
Mycobacterium malmoense	3	0.19%
Other Mycobacteria	3	0.19%
Mycobacterium xenopi	2	0.13%
Mycobacterium lentiflavum	2	0.13%
Mycobacterium scrofulaceum	2	0.13%
Mycobacterium bronchogosinia	2	0.13%
Mycobacterium paragordonae	1	0.06%
Mycobacterium columbiense	1	0.06%
Mycobacterium chelonae	1	0.06%
Mycobacterium chelonae subspecies strain	1	0.06%

NTM, non-tuberculous mycobacteria.

cultured, including 8,936 MTBC and 1,589 NTM strains, with an overall NTM isolation rate of 15.11% (as shown in **Table 1**). The annual isolation rates were 14.39% (547/3,801), 15.61% (521/3,337), and 15.41% (521/3,381) respectively, with no significant differences in detection rates across the years (X^2=2.03, P>0.05).

Among the 1,589 non-tuberculous mycobacteria (NTM) strains, 1,579 were single NTM infections, 8 were mixed infections of Mycobacterium tuberculosis (MTB) and NTM, and 1 involved two different NTM species.

Further species identification revealed 17 types of NTM (to align with advances in NTM research and international standards, the Chinese-named Mycobacterium chelonae ssp. abscessus, 88 strains, were classified as Mycobacterium abscessus). Among the identified strains, there were 1,190 Mycobacterium intracellulare strains, 186 Mycobacterium abscessus strains, 112 Mycobacterium kansasii strains, 45 Mycobacterium avium strains, 12 Mycobacterium gordonae strains, 9 Mycobacterium fortuitum strains, 7 Mycobacterium lentiflavum strains, 3 Mycobacterium malmoense strains, 3 other mycobacteria strains, 2 Mycobacterium xenopi strains, 2 Mycobacterium scrofulaceum strains, 2 Mycobacterium lentiflavum strains, 2 Mycobacterium Gordonia bronchialis strains, 1 Mycobacterium paragordonae strain, 1 Mycobacterium colombiense strain, 1 Mycobacterium chelonae subspecies strain, and 1 Mycobacterium chelonae strain. Additionally, there were 7 mixed infections of Mycobacterium intracellulare and the Mycobacterium tuberculosis complex, 1 mixed infection of Mycobacterium avium and the Mycobacterium tuberculosis complex, and 1 mixed infection of Mycobacterium kansasii and Mycobacterium intracellulare (as shown in **Table 2**). Additionally, 5 strains of Nocardia, 10 strains of Nocardia farcinica, and 1 strain of Nocardia St. George's Chapel were cultured.

The top four most isolated NTM species were Mycobacterium intracellulare (75.36%), Mycobacterium abscessus (11.78%), Mycobacterium kansasii (7.09%), and Mycobacterium avium (2.85%).

Results and sensitivity rates of in vitro drug susceptibility testing (DST)

The drug sensitivity test results for 711 NTM strains from Anhui Chest Hospital between January 2021 and December 2023 were analyzed for sensitivity to 15 antibiotics: clarithromycin, azithromycin, amikacin, rifampicin, rifabutin, cefoxitin, ethambutol, moxifloxacin, linezolid, tobramycin, doxycycline, minocycline, gatifloxacin, sulfamethoxazole, and imipenem/

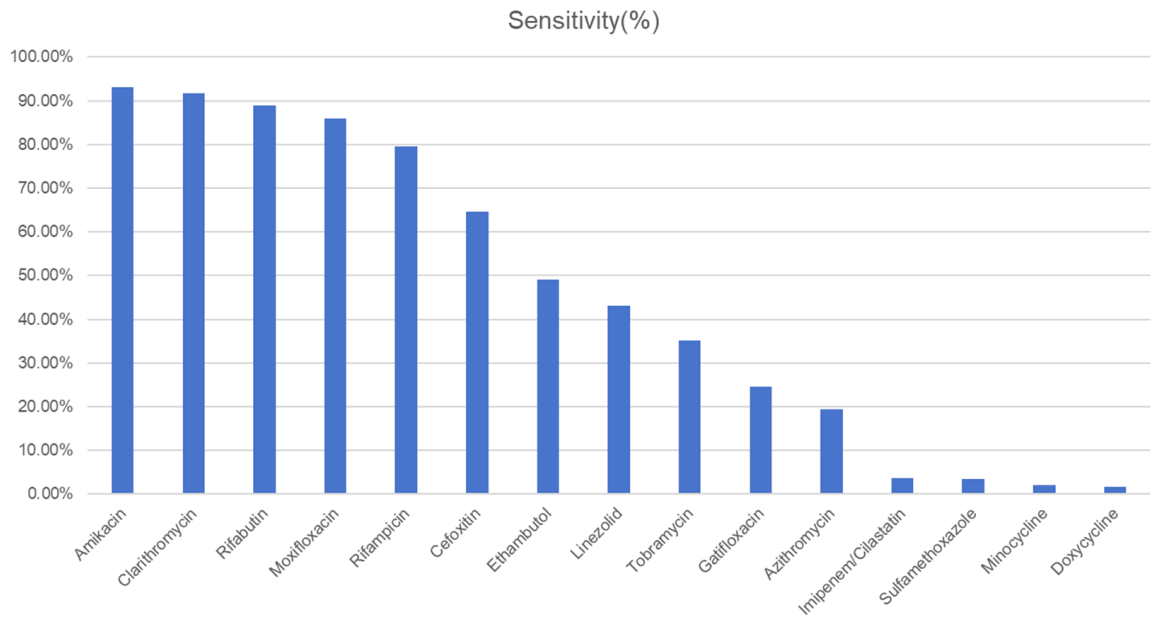

Figure 2. Drug sensitivity rate of non-tuberculous mycobacteria (NTM).

cilastatin. The results showed that NTM exhibited high sensitivity to amikacin and clarithromycin, with sensitivity rates exceeding 90%; additionally, they demonstrated relatively high sensitivity to rifabutin, moxifloxacin, and rifampicin, with sensitivity rates between 89.03% and 79.61%. However, NTM showed high resistance to imipenem/cilastatin, sulfamethoxazole, minocycline, and doxycycline, with sensitivity rates below 4% (as shown in **Figure 2**).

There were differences in drug sensitivity across different NTM species: An analysis of the drug susceptibility test results for the top four most isolated NTM species (**Table 3**).

Mycobacterium intracellulare shows high sensitivity to rifabutin, amikacin, clarithromycin, moxifloxacin, and rifampicin, with sensitivity rates exceeding 90%. It exhibits high resistance to minocycline, doxycycline, imipenem/cilastatin, and sulfamethoxazole, with sensitivity rates below 4%.

Mycobacterium abscessus demonstrates high sensitivity to cefoxitin (91.21%), clarithromycin (85.71%), amikacin (82.42%), and linezolid (60.44%). It shows 100% resistance to ethambutol, and high resistance to doxycycline and sulfamethoxazole (97.8%).

Mycobacterium kansasii shows high sensitivity to rifabutin, clarithromycin, linezolid, moxifloxacin, rifampicin, and amikacin. It has low sensitivity rates to cefoxitin (0.00%), minocycline (1.82%), and tobramycin (1.82%), indicating high resistance.

Mycobacterium avium exhibits higher resistance to azithromycin (5%) and linezolid (10.0%) compared to other NTM species.

Discussion

In recent years, the rapid increase in NTM diseases has become a significant public health concern [14-16]. Currently, in contrast to tuberculosis, there are limited epidemiologic investigation data and research reports on drug susceptibility for non-tuberculous mycobacterial disease. However, China's national tuberculosis epidemiological survey data show that the isolation rate of NTM increased from 4.3% in 1979 and 4.9% in 1990, to 11.1% in 2000 and 22.9% in 2010, showing a continuous upward trend [17]. Consistent with existing research [18], current epidemiologic studies on NTM in China reveal notable regional disparities in both prevalence rates and strain distribution. For instance, the reported NTM isolation rates are 4.6% in Beijing [19], 15.5% in Nanjing [20], 6.2% in Hangzhou [21], 2.21% in Chengdu [22], 30.3% in Guangzhou [23], and 12.1% in Hainan [24]. This study found that the overall isolation rate of NTM in Anhui from 2021 to 2023 was

Table 3. Drug sensitivity analysis of the top 4 NTM species

Drug	Mycobacterium intracellulare (number/ sensitivity rate) n=522	Mycobacterium abscessus (number/ sensitivity rate) n=91	Mycobacterium kansasii (number/ sensitivity rate) n=55	Mycobacterium avium (number/ sensitivity rate) n=20
Rifabutin	510 (97.7%)	37 (40.66%)	55 (100%)	19 (95%)
Amikacin	499 (95.59%)	75 (82.42%)	46 (83.64%)	19 (95%)
Clarithromycin	491 (94.06%)	78 (85.71%)	53 (96.36%)	19 (95%)
Moxifloxacin	490 (93.87%)	31 (34.07%)	50 (90.91%)	18 (90%)
Rifampicin	484 (92.72%)	6 (6.59%)	48 (87.27%)	17 (85%)
Cefoxitin	346 (66.28%)	83 (91.21%)	0 (0%)	15 (75%)
Ethambutol	303 (58.05%)	0 (0%)	33 (60%)	8 (40%)
Tobramycin	225 (43.1%)	11 (12.09%)	1 (1.82%)	8 (40%)
Linezolid	182 (34.87%)	55 (60.44%)	52 (94.55%)	2 (10%)
Gatifloxacin	108 (20.69%)	7 (7.69%)	36 (65.45%)	11 (55%)
Azithromycin	76 (14.56%)	36 (39.56%)	20 (36.36%)	1 (5%)
Sulfamethoxazole	17 (3.26%)	2 (2.2%)	3 (5.45%)	1 (5%)
Imipenem/Cilastatin	14 (2.68%)	3 (3.3%)	4 (7.27%)	1 (5%)
Doxycycline	6 (1.15%)	2 (2.2%)	2 (3.64%)	1 (5%)
Minocycline	4 (0.77%)	6 (6.59%)	1 (1.82%)	1 (5%)

NTM, non-tuberculous mycobacteria.

15.11%, which is at a medium level nationwide.

In terms of epidemiological trends, the NTM isolation rates in Anhui were 14.39% (547/3,801) in 2021, 15.61% (521/3,337) in 2022, and 15.41% (521/3,381) in 2023. The differences in isolation rates between each year were not statistically significant, indicating a stable trend in NTM isolation rate over the three-year period. The incidence of NTM is closely related to age, with rates increasing with age. Additionally, there are differences in the distribution by gender. This study revealed that individuals aged 60 and above accounted for the highest proportion (58.82%, 934/1,588). The male-to-female ratio was 1.28:1, with a higher incidence among males.

This study reveals that the NTM species with the highest isolation proportions in the Anhui region of China (Mycobacterium intracellulare [75.36%], Mycobacterium abscessus [11.78%], Mycobacterium kansasii [7.09%], and Mycobacterium avium [2.85%], with M. intracellulare being the predominant species) are also the most common NTM globally [25, 26]. These data also show some differences from other existing studies in China. In eastern regions such as Hangzhou and Nanjing, the predominant species are predominantly Mycobacterium avium complex (MAC) (66.7% and 70.1% respectively) [20, 21]. In southern areas like Hainan, the predominant species are MAC (29.22%) and Mycobacterium abscessus (19.84%) [24]. In western regions like Chengdu, the predominant species include Mycobacterium avium (26.2%), Mycobacterium abscessus (25.7%), and MAC (24.7%) [22]. In Chongqing city, the predominant species are Mycobacterium abscessus complex (36.3%) and MAC (26.0%) [27]. These variations, in addition to the high variability observed in these studies (i.e. study time, geographic area and methodology, etc.), also explain the significant geographic diversity [28] observed in NTM infections.

NTM exhibits varying degrees of resistance to most antibiotics, and different species show considerable differences in drug sensitivity. The results of this study demonstrate high sensitivity of NTM to amikacin and clarithromycin, with sensitivity rates exceeding 90%. Subsequently, sensitivity rates to rifampicin, moxifloxacin, and levofloxacin range from 89.03% to 79.61%. Sensitivity rates to imipenem/cilastatin, sulfamethoxazole, minocycline, and doxycycline are less than 4%, indicating high resistance. The overall sensitivity rate of NTM to clarithromycin is 91.7%, while the drug sensitivity rate to azithromycin is only 19.41%. Specifically, Mycobacterium intracellulare shows a

sensitivity rate of 14.56% to azithromycin, and Mycobacterium avium demonstrates an even lower sensitivity rate of 5%. These results differ significantly from existing reports on the susceptibility of NTM to azithromycin. This finding may reflect the local epidemiologic characteristics of the Anhui region, which require further investigation. Therefore, caution is advised when selecting azithromycin for NTM treatment in the Anhui region.

This study reports the isolation rate, epidemiological trends, species distribution characteristics, and drug sensitivity of nontuberculous mycobacteria (NTM) in Anhui Province, China. Understanding the current status of NTM disease in Anhui provides reference for the formulation and adjustment of diagnostic and treatment strategies for NTM disease. However, this study also has certain limitations. Further exploration is needed to determine the clinical relevance of isolated NTM strains, the relationship between NTM clinical isolation rate and incidence rate, as well as the clinical characteristics of NTM disease patients, and the relationship between in vitro drug sensitivity test results and actual treatment outcome of NTM disease.

Conclusion

The isolation rate of NTM in Anhui area of China has been stable. Mycobacterium intracellulare is the dominant species (75.36%). NTM strains showed high sensitivity to amikacin, clarithromycin, rifabutin, moxifloxacin, and rifampicin, but high resistance to imipenem/cilastatin, sulfamethoxazole, minocycline, and doxycycline.

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Disclosure of conflict of interest

None.

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