Consensus management recommendations for less common non-tuberculous mycobacterial pulmonary diseases

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The 2020 clinical practice guideline for the treatment of non-tuberculous mycobacterial pulmonary disease (NTM-PD) by the American Thoracic Society, European Respiratory Society, European Society of Clinical Microbiology and Infectious Diseases, and Infectious Diseases Society of America; and the 2017 management guideline by the British Thoracic Society covered pulmonary diseases in adults caused by *Mycobacterium avium* complex, *Mycobacterium kansasii*, *Mycobacterium xenopi*, and *Mycobacterium abscessus*. In order to provide evidence-based recommendations for the treatment of less common non-tuberculous mycobacterial (NTM) species in adult patients without cystic fibrosis or HIV infection, our expert panel group performed systematic literature searches to provide management guidance for pulmonary diseases caused by seven additional organisms: *Mycobacterium chelonae*, *Mycobacterium fortuitum*, *Mycobacterium genavense*, *Mycobacterium gordonae*, *Mycobacterium malmoense*, *Mycobacterium simiae*, and *Mycobacterium szulgai*. Treatment recommendations were developed by a structured consensus process. The evidence from the scientific literature published in English for treatment recommendations for pulmonary diseases caused by other NTM species was of very low quality, with the exception of *M malmoense*, and based on the evaluation of case reports and case series. For *M malmoense*, results from two randomised controlled trials and three retrospective cohort studies provided a better evidence base for treatment recommendations, although the evidence was still of low quality.

Introduction

The 2020 updated management guideline for patients with non-tuberculous mycobacterial pulmonary diseases (NTM-PD) focuses on population, intervention, comparison, and outcome question-guided management recommendations for pulmonary disease in adults caused by *Mycobacterium avium* complex, *Mycobacterium kansasii*, *Mycobacterium xenopi*, and *Mycobacterium abscessus*.[1,2] However, management options for NTM-PD caused by other clinically relevant non-tuberculous mycobacteria (NTM) covered in the previous management guideline are also needed for the care of affected patients.[3] At present, treatment recommendations for patients with other NTM-PDs are primarily based on expert opinions and often variable. Health-care providers of patients with NTM-PDs should consult with a clinical microbiologist who has expertise in identification and antimycobacterial drug susceptibility testing, and a clinician with expertise in managing NTM disease. However, evidence-based management decisions are needed for patients affected by NTM not covered in the 2017 guideline by the British Thoracic Society (BTS) or the 2020 American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Microbiology and Clinical Infectious Diseases (ESCMID), and Infectious Diseases Society of America (IDSA) guideline.[4]

The panel of members of the 2020 ATS, ERS, ESCMID, and IDSA guideline committee did systematic reviews of the literature, independently of the societies involved in the original task force, to provide management guidance for pulmonary diseases caused by seven additional organisms: *Mycobacterium chelonae*, *Mycobacterium fortuitum*, *Mycobacterium genavense*, *Mycobacterium gordonae*, *Mycobacterium malmoense*, *Mycobacterium simiae*, and *Mycobacterium szulgai*.

The following consensus guidance includes recommendations for antibiotics guided by in-vitro susceptibility results. With the exception of *M chelonae* and *M fortuitum*, there are no validated break points defining susceptibility and resistance for any of the antibiotics used for the organisms considered here.[5]

Methods

A search (see appendix pp 4–7) was adapted for execution on the Ovid MEDLINE platform and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Embase, and the Cochrane Central Register of Controlled Trials. Searches were limited to human studies or studies indexed with neither human nor animal and those published in English. A final update was executed on Jan 6, 2020. Teams of two or three independent experts evaluated the search results for eligibility; they supplemented the electronic search by contacting experts and handsearching journals, conference proceedings, reference lists, and regulatory agency websites for relevant articles.

In addition to the systematic reviews, the members of the panel ascertained agreement on management options in a six-step consensus process as previously published.[6-8] The results of the panel experts' votes, either in favour or against the treatment approach, is presented in the appendix (appendix p 1).

General recommendations

The expert panel recommends that health-care providers consult with a clinical microbiologist who has expertise

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See Online for appendix

Panel: **Clinical and microbiological criteria for diagnosis of non-tuberculous mycobacteria**

Clinical

Pulmonary or systemic symptoms; and nodular or cavitary opacities on chest radiograph or a high-resolution computed tomography scan that shows bronchiectasis with multiple small nodules and appropriate exclusion of other diagnoses.

Microbiological*

- Positive culture results for a non-tuberculous mycobacteria (NTM) from at least two separate expectorated sputum samples. If the results are nondiagnostic, consider repeat sputum acid-fast bacilli smears and cultures.

or

- Positive culture results for a NTM from at least one bronchial wash or lavage.

or

- Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or acid-fast bacilli) and positive culture for NTM or biopsy showing mycobacterial histologic features (granulomatous inflammation or acid-fast bacilli) and one or more expectorated sputum or bronchial washings that are culture positive for NTM.

Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination. Patients who are suspected of having NTM pulmonary disease but do not meet the diagnostic criteria should be followed up until the diagnosis is firmly established or excluded. Making the diagnosis of NTM pulmonary disease does not per se, necessitate the institution of therapy, which is a decision based on the potential risks and benefits of therapy for individual patients.

*When two positive cultures are obtained, the isolates should be the same NTM species in order to meet disease criteria.

in identification and antimycobacterial drug susceptibility testing. Patients should be referred to a clinician with expertise in managing NTM-PD before treatment against any of the mycobacterial pathogens described in this consensus document is initiated. The clinical and microbiological criteria for the diagnosis of NTM-PD are displayed in panel.

The choice of treatment regimen should be guided by the results of the antimycobacterial drug susceptibility testing, although for some species causing NTM-PD—ie, *M genavense* and *M simiae*—the correlation of antimycobacterial drug susceptibility testing and clinical outcome can be poor (figure). For orientation, the minimum inhibitory concentrations (MIC) of antibiotics against select NTM species required to inhibit the growth of 50% and 90% of organisms (MIC50 and MIC90) are provided in the appendix (appendix p 2). The major contributions of the mycobacteriology laboratory are to correctly identify the NTM species, perform antimycobacterial drug susceptibility testing, and detect acquired and inducible resistance. The dosing of drugs for the treatment of NTM-PDs mentioned in this document follows recent ATS, ERS, ESCMID, and IDSA recommendations (table 1).[1,2] Treatment considerations are summarised in tables 2 and 3 and the quality of the evidence and strength of the recommendations are displayed in the appendix (appendix p 3)

To monitor treatment (supplement table 2, appendix p 3), sputum samples should be collected for culture every 1–2 months after initiation of therapy until there is sputum conversion to culture negative (at least two consecutive negative mycobacterial sputum cultures, collected at least 4 weeks apart during antibiotic treatment); the sampling date of the first negative culture is the date of sputum conversion to culture negative.[6] Thereafter, sputum should be collected every 2–3 months until therapy is completed, defined as 12 months of negative mycobacterial sputum cultures (while on therapy) from the date of the first negative culture.

Rapidly growing NTM

M chelonae

M chelonae is an unusual cause of NTM-PD;[3,9,10] therefore, clinicians should carefully assess for other causes of the patients symptoms and verify fulfillment of disease criteria before embarking on a course of treatment. Isolates are usually susceptible to tobramycin, macrolides (eg, clarithromycin and azithromycin), clofazimine, linezolid, and sometimes to fluoroquinolones and imipenem.[3,11–15] Tobramycin is more active in vitro than amikacin and *M chelonae* is generally resistant to cefoxitin.[16] *M chelonae* does not contain an erythromycin resistance methylase (*erm*) gene,[17] so the macrolides are considered fully active, unlike *M fortuitum* and some *M abscessus* subspecies, which have functional *erm* genes. Antimycobacterial drug susceptibility testing should be done, as well as detection of acquired resistance to macrolides, which was described in this species, although mostly in non-pulmonary infections.[18]

A systematic literature review by two independent experts identified 18 case reports and case series describing 57 patients with *M chelonae* pulmonary disease in the scientific literature published in English, but no evidence-based management recommendations for *M chelonae* pulmonary disease based on clinical trial data.[9,14,19–34] In most patients, risk factors for *M chelonae* pulmonary disease were not stated or could not be identified. Approximately 15% of patients who have been reported with *M chelonae* pulmonary disease were post-organ transplant.[19,21,23] By contrast with *M fortuitum* pulmonary disease, gastrointestinal motility disorders (eg, achalasia) did not appear to be a prominent risk

factor for *M chelonae* pulmonary disease. The clinical spectrum of *M chelonae* pulmonary disease includes bronchiolitis, fibronodular or patchy consolidations, cavitary disease, and rarely empyema.

Treatment for *M chelonae* pulmonary disease initially includes at least two drugs for mild to moderate disease or three drugs in more severe disease that the organism shows in-vitro susceptibility to. Treatment often includes one or two intravenous drugs to be continued for an initial period, usually for 4–16 weeks, to achieve control of disease; tobramycin is the preferred aminoglycoside. At least two oral drugs, one of which should be a macrolide that has demonstrated in-vitro susceptibility, are administered for a total duration of therapy of at least 12 months after conversion to culture negative, to complete the treatment regimen.

Favoured antibiotics include azithromycin (250–500 mg) once a day or clarithromycin (500 mg) twice a day, tobramycin (4·5–7 mg/kg) intravenously once a day or tobramycin (5–7 mg/kg) intravenously three times a week, imipenem-cilastatin (1 g each) intravenously two or three times a day or a fluoroquinolone—eg, moxifloxacin (400 mg) once a day—clofazimine (100–200 mg) once a day, or linezolid (600 mg) once a day, based on in-vitro antimycobacterial drug susceptibility test results. Caution must be exercised in the prolonged use of aminoglycosides because of the risk of otovestibular toxicity and nephrotoxicity. Approximately 20% of patients with *M chelonae* pulmonary disease received adjunctive partial pulmonary surgical resection;[20,25] these patients generally had a successful treatment outcome, thus surgical resection should be considered when it is an option. Based on the available literature, it was not possible to state an association between the type of drug therapy against *M chelonae* pulmonary disease and successful treatment outcome.

M fortuitum

Although *M fortuitum* is a relatively common NTM species isolated from respiratory specimens, it is a relatively uncommon cause of NTM-PD.[3,9,35] Clinicians should maintain a high-diagnostic threshold for identifying *M fortuitum* pulmonary disease, and they should carefully assess for other causes of the patients symptoms and radiological abnormalities. *M fortuitum* isolates are usually susceptible to multiple antibiotics including fluoroquinolones, doxycycline, minocycline, and sulfonamides.[3] In-vitro data suggest susceptibility to clofazimine (appendix p 2). In addition, isolates are typically susceptible to amikacin and imipenem. *M fortuitum* usually contains an *erm* (39) gene which confers inducible resistance; therefore, macrolides should not be considered active.[36] Antimycobacterial drug susceptibility testing should be done, as well as detection of acquired resistance to fluoroquinolones, which was described in this species, although mostly in non-pulmonary infections.[37]

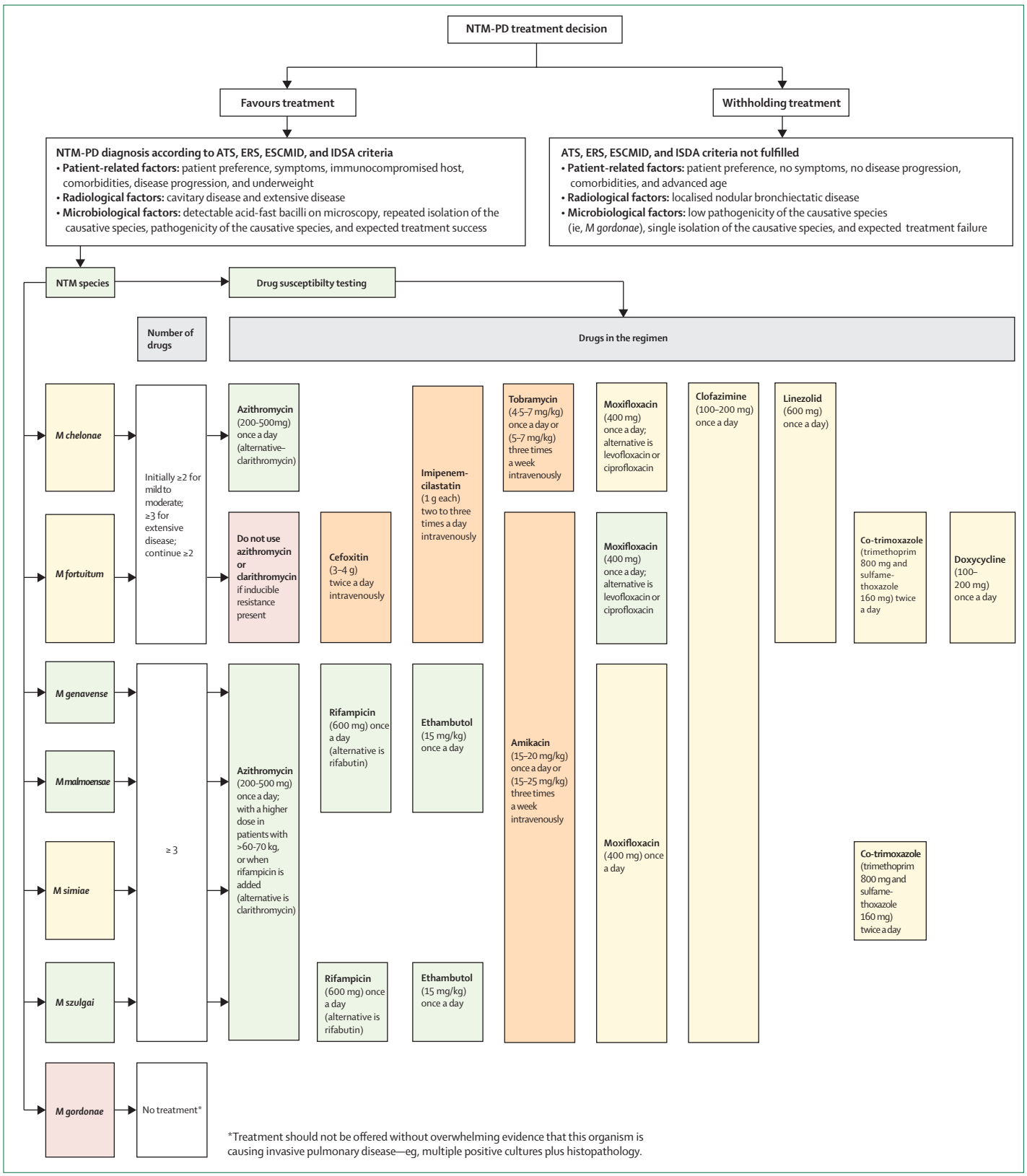
A systematic literature review by two independent experts identified 45 case reports and case series describing 150 patients with *M fortuitum* pulmonary disease in the scientific literature published in English, but no evidence-based management recommendations based on clinical trial data for *M fortuitum* pulmonary disease.[11,19,21,24,26,28,29,31,32,34,35,38–71]

M fortuitum pulmonary disease occurs predominantly in patients with underlying conditions: oesophageal and gastrointestinal motility problems (eg, achalasia),[40,41,45] structural lung changes such as post-tuberculosis changes[35,38,54] severe chronic obstructive pulmonary disease (COPD),[58,69] and cancer.[24,58] Conversion to sputum culture negative for *M fortuitum* without antibiotic treatment is not uncommon when the underlying cause (eg, achalasia) has been addressed.[9] The underlying cause must be addressed if possible; with its correction or improvement, antibiotic treatment might not be required, or a less intensive regimen might suffice. However, *M fortuitum* pulmonary disease is associated with a poor prognosis and about a-third of the affected patients reported in the literature do not survive despite antibiotic therapy, probably reflecting the severity of the underlying disease.[28,45,58,68,71]

Patients who received fluoroquinolones as part of their treatment regimen seemed to have a favourable treatment outcome, but we did not find any publications that met the criteria of a clinical trial for evidence-based management recommendations for *M fortuitum* pulmonary disease.[38,42,53,54,56,58,63,67]

Clinicians should be aware that there are other mycobacterial species related to *M fortuitum* (*Mycobacterim peregrinum, Mycobacterim septicum, Mycobacterim porcinum,* and *Mycobacterim conceptionense*) included in the so-called *M fortuitum* complex, which might present different antibiotic susceptibilities, including macrolide susceptibility.[72]

Treatment for *M fortuitum* pulmonary disease should include at least two drugs for mild-to-moderate disease or three drugs in more severe disease that the organism shows in-vitro susceptibility to. Treatment often includes one or two intravenous drugs to be continued for an initial period, usually for 4–16 weeks, to achieve control of disease; amikacin is the preferred aminoglycoside. Frequently used doses include amikacin (15–20 mg/kg) intravenously once a day or amikacin (15–25 mg/kg) three times a week in severe disease manifestations (lower in older patients and in prolonged treatment). Caution must be exercised in the prolonged use of aminoglycosides because of the risk of otovestibular toxicity and nephrotoxicity. Other favoured intravenous drugs are imipenem-cilastatin (1 g each) intravenously two or three times a day or cefoxitin (3–4 g) intravenously twice a day. At least two oral drugs that have demonstrated in-vitro susceptibility should be continued until at least 12 months after conversion to culture negative to complete the treatment regimen. Favoured oral


NTM-PD treatment decision
Favours treatment
Withholding treatment
NTM-PD diagnosis according to ATS, ERS, ESCMID, and IDSA criteria
• Patient-related factors: patient preference, symptoms, immunocompromised host, comorbidities, disease progression, and underweight
• Radiological factors: cavitary disease and extensive disease
• Microbiological factors: detectable acid-fast bacilli on microscopy, repeated isolation of the causative species, pathogenicity of the causative species, and expected treatment success
ATS, ERS, ESCMID, and ISDA criteria not fulfilled
• Patient-related factors: patient preference, no symptoms, no disease progression, comorbidities, and advanced age
• Radiological factors: localised nodular bronchiectatic disease
• Microbiological factors: low pathogenicity of the causative species (ie, M gordonae), single isolation of the causative species, and expected treatment failure
NTM species
Drug susceptibilty testing
Number of drugs
Drugs in the regimen
M chelonae
M fortuitum
M genavense
M malmoense
M simiae
M szulgai
M gordonae
Initially ≥2 for mild to moderate; ≥3 for extensive disease; continue ≥2
≥ 3
No treatment*
Azithromycin (200-500mg) once a day (alternative–clarithromycin)
Do not use azithromycin or clarithromycin if inducible resistance present
Azithromycin (200-500 mg) once a day; with a higher dose in patients with >60-70 kg, or when rifampicin is added (alternative is clarithromycin)
Cefoxitin (3–4 g) twice a day intravenously
Rifampicin (600 mg) once a day (alternative is rifabutin)
Rifampicin (600 mg) once a day (alternative is rifabutin)
Imipenem-cilastatin (1 g each) two to three times a day intravenously
Ethambutol (15 mg/kg) once a day
Ethambutol (15 mg/kg) once a day
Tobramycin (4·5–7 mg/kg) once a day or (5–7 mg/kg) three times a week intravenously
Amikacin (15–20 mg/kg) once a day or (15–25 mg/kg) three times a week intravenously
Moxifloxacin (400 mg) once a day; alternative is levofloxacin or ciprofloxacin
Moxifloxacin (400 mg) once a day; alternative is levofloxacin or ciprofloxacin
Moxifloxacin (400 mg) once a day
Clofazimine (100–200 mg) once a day
Linezolid (600 mg) once a day)
Co-trimoxazole (trimethoprim 800 mg and sulfame-thoxazole 160 mg) twice a day
Co-trimoxazole (trimethoprim 800 mg and sulfame-thoxazole 160 mg) twice a day
Doxycycline (100–200 mg) once a day
*Treatment should not be offered without overwhelming evidence that this organism is causing invasive pulmonary disease—eg, multiple positive cultures plus histopathology.

antibiotics include fluoroquinolones—eg, moxifloxacin (400 mg) once a day or levofloxacin (750–1000 mg) once a day—co-trimoxazole (trimethoprim 800 mg and 160 mg sulfamethoxazole) twice a day, linezolid (600 mg) once a day, clofazimine (100–200 mg) once a day, or doxycycline (100–200 mg) once a day. A summary of rapidly growing NTM treatment recommendations is shown in table 2.

Slowly growing NTM

M genavense

M genavense is a rare cause of NTM-PD.[73–75] The organism is fastidious and does not grow on solid media, although limited growth can be observed in supplemented broth cultures; molecular detection is most reliable, thus antimycobacterial drug susceptibility testing in *M genavense* is challenging.[76] A systematic literature review by two independent experts identified five case reports and case series describing six patients with *M genavense* pulmonary disease in the scientific literature published in English, but no clinical trial data to inform evidence-based management recommendations for *M genavense* pulmonary disease.[73,77-79] *M genavense* was first described in the setting of severe immunosuppression with disseminated disease.[3,74,75,80]

Available data suggests that most isolates are susceptible in vitro to fluoroquinolones, clofazimine, and amikacin, although susceptibility testing has not been standardised for *M genavense* (appendix p 2).[80,81] Case series have described treatment success with macrolide containing multi-drug regimens that typically include ethambutol plus one or two other drugs such as a rifamycin, amikacin, or a fluoroquinolone.[74,75,82-84]

Treatment for *M genavense* pulmonary disease includes at least three drugs that the organism shows in-vitro susceptibility to. The panel suggests the following treatment regimen: azithromycin (250–500 mg) once a day, rifampicin (600 mg) once a day, and ethambutol (15 mg/kg) once a day. In case of intolerance or drug resistance to macrolides, rifamycins, or ethambutol, the following treatment regime can be used instead: moxifloxacin (400 mg) once a day, amikacin (15–20 mg/kg) intravenously once a day or amikacin (15–25 mg/kg) three times a week (lower in older patients and prolonged use), or clofazimine (100–200 mg) once a day. Treatment should be continued until at least 12 months post-conversion to culture negative to complete the treatment regimen.

M gordonae

M gordonae is known as a non-pathogenic species but is one of the most common NTM isolated from respiratory samples; probably because it is prevalent in the environment, especially the water supply network.[85–89] It is also easily isolated in mycobacteriology laboratories (naturally orange colonies growing on all media after 2 weeks incubation). Limited data suggest that *M gordonae* is variably susceptible in vitro to several agents: clarithromycin, ciprofloxacin, linezolid, and amikacin.[90-92] The correlation between these in-vitro results and patient outcomes is unknown.

A systematic literature review by two independent experts identified nine case reports and case series describing 13 non-immunosuppressed adults with *M gordonae* pulmonary disease in whom treatment and outcomes were adequately described, but no evidence-based management recommendations for *M gordonae* pulmonary disease based on clinical trial data.[69,93-100]

Treatment for *M gordonae* pulmonary disease before 1990 often included isoniazid, rifampicin, and ethambutol. Treatment in newer studies more frequently included clarithromycin, rifampicin, and ethambutol. Information regarding cure was provided for 12 cases and was definite or likely in 11 (92%) patients overall and 11 patients who did not experience respiratory failure.[69,93-100] Surgical resection, in addition to antibiotic therapy, was described in two patients, both of whom were cured.[97,100]

When *M gordonae* is cultured in respiratory samples, other causes of lung disease should be carefully considered. Multiple sputum samples should be collected over several weeks or months to identify the presence of any other NTM known to be more pathogenic. Clinicians should maintain a high-diagnostic threshold for identifying *M gordonae* pulmonary disease. In addition to the clinical and radiological criteria for *M gordonae* pulmonary disease (as *M gordonae* is almost always non-pathogenic) described in the international NTM guidelines,[97] more than two positive sputum cultures and at least one detection of acid-fast bacilli in a respiratory specimen with documented *M gordonae* cultures should be present.

Even when current diagnostic criteria are met, treatment is seldom necessary. In the rare situation when treatment is necessary, antimycobacterial drug susceptibility testing can be done as for other NTM; although no standard treatment can be recommended, a combination of a macrolide, rifampicin, and ethambutol has been described as successful in some cases.

Figure: **Optimal treatment pathways for less commonly encountered NTM-PD**

The flow chart provides information on the recommended treatment for seven less common NTM. The seven species of NTM are displayed in the left-hand column of the flow chart; species coloured in green indicate high pathogenicity and high probability of causing disease, yellow indicates species which are less pathogenic with a lower probability of causing disease, and red indicated a species that likely represents a contaminant. Drugs used to treat the NTM are displayed to the right of the flow chart; green indicates drugs that are most strongly recommended, yellow indicates less certainty due to missing clinical data, orange indicates drugs that have to be given intravenously, thus are not preferred, and red indicates drugs that should not be used. NTM= non-tuberculous mycobacteria. NTM-PD=non-tuberculous mycobacterial pulmonary disease. ATS=American Thoracic Society. ERS=European Respiratory Society. ESCMID=European Society of Clinical Microbiology and Infectious Diseases. IDSA=Infectious Disease Society of America. Please see appendix for additional information (appendix p 8).

	Daily dose	Three times a week dose	Hepatic impairment dose	Renal impairment dose
Oral				
Azithromycin	250–500 mg once a day	500 mg once a day	NA	NA
Ciprofloxacin	500–750 mg twice a day	NA	NA	250–500 mg dosed at intervals according to CrCl
Clarithromycin	500 mg twice a day	500 mg once a day	NA	Reduce dose by 50% if CrCl less than 30 mL/min
Clofazimine*	100–200 mg once a day	NA	Caution in severe hepatic impairment	NA
Doxycycline	100 mg once a day or twice a day	NA	NA	NA
Ethambutol	15 mg/kg once a day	25 mg/kg once a day	NA	Increase dosing interval (eg, 15–25 mg/kg, three times a week)
Levofloxacin	750–1000 mg once a day	NA	NA	Increase dosing interval (eg, 10–15 mg/kg, three times a week)
Linezolid	600 mg once a day or twice a day†	NA	NA	NA
Moxifloxacin	400 mg once a day	NA	NA	NA
Rifabutin	150–300 mg once a day (150 mg once a day with clarithromycin)	300 mg once a day	Caution	Reduce dose by 50% if CrCl less than 30 mL/min
Rifampicin	10 mg/kg (450 mg or 600 mg) once a day	600 mg once a day	Caution	NA
Co-trimoxazole	800 mg trimethoprim and 160 mg sulfamethoxazole twice a day	NA	Caution	Reduce dose by 50% if CrCl 15–30 mL/min
Parenteral				
Amikacin‡ (IV)	15–20 mg/kg once a day§, adjusted according to drug level monitoring¶	15–25 mg/kg once a day§, adjusted according to drug level monitoring¶	NA	Reduce dose or increase dosing interval (eg, 15 mg/kg, twice a week or three times a week)
Cefoxitin (IV)	2–4 g twice a day or three times a day (maximum daily dose is 12 g/day)	NA	NA	Reduce dose or increase dosing interval
Imipenem-cilastatin (IV)	1g each, twice a day or three times a day	NA	NA	Reduce dose or increase dosing interval
Tobramycin‡ (IV)	4.5–7 mg/kg once a day	5–7 mg/kg once a day	NA	Reduce dose or increase dosing interval (eg, 5–7 mg/kg, twice a week or three times a week); inhalative route of administration not studied

NA=not applicable. NTM-PD= non-tuberculous mycobacterial pulmonary disease. CrCl= creatinine clearance. IV=intravenously. This table should be considered as a general guide for dosing in clinical practice, and it does not replace specific local, national, or regional dosing guidelines. *Clofazimine availability varies by country. In the USA, an investigational new drug application is required. †Most experts recommend once a day dosing of linezolid because of the high rate of drug-related adverse reactions associated with twice a day dosing. ‡Caution must be exercised in the prolonged use of aminoglycosides because of the risk of otovestibular toxicity and nephrotoxicity. §The use of the described regimens for 15 weeks was associated with permanent ototoxicity in approximately a-third of patients, and the risk was associated with age and cumulative dose. Given the high rates of ototoxicity, risks and benefits should be carefully considered with the aims of therapy. Clinicians should consider lower dose ranges and probably rely on intermittent dosing when more prolonged therapy is employed. ¶Drug level monitoring: trough less than 5 mg/L, peak with daily dosing 35–45 µg/mL, peak with intermittent dosing 65–80 µg/mL.

Table 1: **Dosing guidelines for drugs used in the management of NTM-PD**

M malmoense

M malmoense was first described in four patients from Malmö and Lund, Sweden,[101] in 1977 and is one of the most common species causing NTM-PD in regions of northern Europe. Multiple studies using different laboratory methods have described the susceptibility of *M malmoense* to rifampicin, rifabutin, clarithromycin, and clofazimine, with variable resistance to amikacin, ethambutol, and fluoroquinolones, and resistance to isoniazid.[102–106]

M malmoense most commonly causes pulmonary disease but can also cause cervical lymphadenitis, tenosynovitis, skin infections, and rarely disseminated disease in the severely immunocompromised host. It is seldom isolated from the environment but it can be found in natural water and soil in some geographical areas.[107–109] The clinical presentation of *M malmoense* pulmonary disease frequently mimics tuberculosis, with cavities and airspace disease being the most common radiological findings.[110,111] The majority of affected patients are male, approximately half have underlying COPD or a history of pulmonary tuberculosis. When *M malmoense* is isolated from respiratory samples, it is usually of clinical significance, although there is some geographical

	Number of drugs	Drugs	Duration of therapy	Comments
M chelonae	Initial phase (≥3); continuation phase (≥2)	Azithromycin (once a day) or clarithromycin (twice a day); tobramycin IV (once a day or three times a week); imipenem-cilastatin (two to three times a day); moxifloxacin (once a day) or levofloxacin (once a day), or ciprofloxacin (twice a day); linezolid (once a day); clofazamine (once a day)	12 months beyond culture conversion	Very low level of evidence; drugs should be selected according to DST results when available; caution patients about aminoglycoside ototoxicity and nephrotoxicity; for mild to moderate disease an oral two-drug regimen could suffice, provided that DST has proven two such drugs to be active
M fortuitum	Initial phase (≥3); continuation phase (≥2)	Moxifloxacin (once a day) or levofloxacin (once a day), or ciprofloxacin (twice a day); amikacin IV (once a day or three times a week); imipenem-cilastatin (two to three times a day); cefoxitin (two to three times a day); linezolid (once a day); co-trimoxazole (twice a day); (clofazimine [once a day]); (doxycycline [twice a day])*	12 months beyond culture conversion	Very low level of evidence; drugs should be selected according to DST results when available; the detection and management of underlying oesophageal disorders or aspiration is critical; fluoroquinolones are probably the most effective; there is natural resistance to macrolides; caution patients about ototoxicity and nephrotoxicity of aminoglycosides; for mild to moderate disease an oral two-drug regimen could suffice provided that DST has proven two such drugs to be active

NTM-PD=non-tuberculous mycobacterial pulmonary disease. IV=intravenously. DST=drug susceptibility testing.*Drugs in brackets are non-preferred options.

Table 2: **Treatment regimens for rapidly growing NTM-PD**

	Number of drugs	Drugs*	Duration of therapy	Comments
M genavense	≥3	Azithromycin (once a day) or (clarithromycin [twice a day]); rifampicin (once a day); ethambutol (once a day); (moxifloxacin [once a day]); (clofazimine [once a day]); (amikacin IV [once a day])	12 months beyond culture conversion	Very low level of evidence; drugs should be selected according to DST results when available; moxifloxacin or amikacin may be used in cases of intolerance or drug resistance to macrolides, rifamycins, or ethambutol
M malmoense	≥3	Azithromycin (once a day) or (clarithromycin [twice a day]); rifampicin (once a day); ethambutol (once a day); (amikacin IV [once a day or three times a week]); (moxifloxacin [once a day]); (clofazimine [once a day])	12 months beyond culture conversion	Low level of evidence; drugs should be selected according to DST results, when available; moxifloxacin or clofazimine can be used in case of intolerance or drug resistance to macrolides, rifamycins, or ethambutol; amikacin should be added for cavitary or severe disease; caution patients about aminoglycoside ototoxicity and nephrotoxicity
M szulgai	≥3	Azithromycin (once a day) or (clarithromycin [twice a day]); rifampicin (once a day); ethambutol (once a day); (moxifloxacin [once a day]); (clofazimine [once a day]); (amikacin IV [once a day or three times a week])	12 months or 12 months beyond culture conversion if treatment with a macrolide, a rifamycin, or ethambutol cannot be used.	Very low level of evidence; drugs should be selected according to DST results, when available; fluoroquinolones (moxifloxacin or levofloxacin), clofazimine, or aminoglycosides (streptomycin or amikacin) can be used in case of intolerance or drug resistance to macrolides, rifamycins, or ethambutol; caution patients about ototoxicity and nephrotoxicity of aminoglycosides
M simiae	≥3	Azithromycin or (clarithromycin); moxifloxacin (once a day); co-trimoxazole (twice a day); clofazimine (once a day); (amikacin IV [once a day or three times a week])	12 months beyond culture conversion	Very low level of evidence; drugs should be selected according to DST results, when available; amikacin should be added for cavitary or severe disease; possible combinations include azithromycin, moxifloxacin, and co-trimoxazole; azithromycin, clofazimine, and amikacin; or azithromycin and moxifloxacin in combination with one or two additional drugs based on DST results with clofazimine and amikacin being the most suitable options
M gordonae†	NA	NA	NA	NA

IV=intravenously. DST=drug susceptibility testing. NA=not applicable. *Drugs in brackets are non-preferred options. †In general, isolation of *M gordonae* from respiratory specimens represents transient colonisation or laboratory contamination; treatment should not be offered without overwhelming evidence that this organism is causing invasive pulmonary disease. If treatment is necessary, DST can be performed; although no standard treatment can be recommended, a combination of a macrolide, rifampicin, and ethambutol has been described as successful.

Table 3: **Treatment regimens for slowly growing NTM-PD**

variability suggesting that pathogenicity might vary by region.[102,112]

A systematic literature review by two independent experts found five publications (two randomised controlled trials[104,105] and three retrospective cohort studies[102,113,114]) that met criteria for evidence-based management recommendations for *M malmoense* pulmonary disease. In addition, two systematic reviews were identified that addressed treatment outcomes or treatment recommendations for *M malmoense* pulmonary disease.[4,48]

An early retrospective review[113] from Cardiff, UK, described the clinical outcomes of 37 patients with *M malmoense* pulmonary disease who were treated with a variety of non-macrolide-based treatment regimens. Those who received three drugs (isoniazid, rifampicin, and ethambutol) for 18–24 months tended to do better than those who received two drugs, or those who were treated for less than 18 months.[113] Among patients treated with a BTS recommended regimen (rifampicin plus different combinations of ethambutol, isoniazid, clarithromycin, or ciprofloxacin) treatment success was achieved in 75% of patients. In a series of 14 consecutive patients with fibrocavitary *M malmoense* pulmonary disease in Edinburgh, UK, investigators reported 100% conversion to culture negative and symptom reduction after 24 months of combination rifampicin

(450–600 mg) once a day, ethambutol (15 mg/kg) once a day, and clarithromycin (500 mg) twice a day.[114] In this study initial *M malmoense* isolates from all 14 patients were judged to be susceptible to rifampicin and resistant to isoniazid, with 23% resistant to ethambutol, 8% resistant to clarithromycin, and 46% resistant to ciprofloxacin. A retrospective review of 30 patients with *M malmoense* pulmonary disease from the Netherlands found that multi-drug treatment regimens varied considerably, although most received a macrolide in addition to ethambutol and rifampicin.[102] The mean duration of therapy was 12 months, which is shorter than the duration in the BTS trials. 21 (70%) patients had a good clinical response (defined as symptomatic improvement and conversion to culture negative) to treatment, five (17%) patients had failure or relapse, and four (13%) patients died.

The BTS performed a randomised controlled trial involving 106 patients with *M malmoense* pulmonary disease; patients were treated for 2 years with either rifampicin and ethambutol or rifampicin, ethambutol, and isoniazid.[104,105] Of 106 patients, 10% of patients had a poor clinical outcome (death due to NTM, treatment failure, or relapse); there was no significant difference between groups. Only 20 (38%) of 52 patients who received rifampicin and ethambutol, and 24 (44%) of 54 of patients who additionally received isoniazid were alive and free of relapse, and therefore considered cured after 5 years. A second BTS randomised controlled trial allocated 167 patients to 2 years of treatment with rifampicin, ethambutol, and clarithromycin; or rifampicin, ethambutol, and ciprofloxacin. [115] Although there was no significant difference in the poor outcome rate between groups (overall, 7%), more patients receiving the rifampicin, ethambutol, and clarithromycin regimen completed treatment and were alive and cured at 5 years (38% *vs* 20%); however, there were more side effects in this group. In addition, the number of patients alive and cured at 5 years in the clarithromycin group was the same as that seen with rifampicin and ethambutol in the previous trial. Compared with patients with *M avium* complex and *M xenopi* pulmonary disease, who were also included in the trial, patients with *M malmoense* were significantly less likely to have a poor outcome.

Two systematic reviews were identified.[4,48] One systematic review reported that three studies[105,114,115] investigated treatment outcomes in patients with *M malmoense* pulmonary disease, comprising a total of 287 patients.[48] The weighted average proportion of treatment success (the proportion of patients in whom sputum conversion to culture negative was achieved at the end of therapy minus the proportion of relapses reported at the end of follow-up) was 54·4% (95% CI 34·7–73·4); however, the authors noted that the comparability between the studies and the different treatment regimens was impeded by the high all-cause mortality of 34–49·1%.

The BTS NTM guideline reviewed two randomised controlled trials[104,115] and four case series.[102,103,113,114] For non-cavitary disease the recommended treatment was with a macrolide, rifampicin, and ethambutol. The addition of parenteral or inhaled amikacin was recommended in cavitary disease, although there was no evidence presented that supported the use of amikacin.[4] A macrolide-containing three-drug regimen offers the best option for treatment success based on these studies, although treatment outcomes remain suboptimal and the evidence base for treatment recommendations is low.

Treatment for *M malmoense* pulmonary disease generally includes at least three drugs: azithromycin (250–500 mg) once a day or clarithromycin (500 mg) twice a day, rifampicin (600 mg) once a day, and ethambutol (15 mg/kg) once a day. Additional drugs may include moxifloxacin (400 mg) once a day or clofazimine (100–200 mg) once a day. Based on the utility of amikacin for most NTM species (except *M chelonae*), favourable in-vitro drug susceptibility profiles, and expert opinion, the addition of parenteral amikacin can be considered in severe cases, such as cavitary disease. The optimal duration of therapy is unknown, but consistent with other NTM pulmonary pathogens the expert panel recommends a total duration of therapy of at least 12 months post-conversion to culture negative to complete the treatment regimen.

M simiae

M simiae is a rare human pathogen causing disseminated or pulmonary disease; only 4–21% of patients with respiratory *M simiae* isolates fulfil the ATS diagnostic criteria.[116-118] The rates of isolation vary geographically[119] with higher rates being reported in Israel[120,121], Lebanon[122], Iran[123] and India.[124] Respiratory isolates of *M simiae* are most often contaminants, thus clinicians should maintain a high threshold to diagnose *M simiae* pulmonary disease and carefully assess for other causes of a patient's symptoms or radiological abnormalities. *M simiae* is considered among the hardest to treat NTM owing to its natural drug resistance; most antimycobacterial drug susceptibility testing reports of *M simiae* describe resistance to most tested drugs.[116,118,125] In vitro, the *M simiae* strain ATCC 25275 was resistant to most of the 19 drugs tested, except macrolides, clofazimine, and sulfamethoxazole (quinolones and aminoglycosides were not tested).[126] Furthermore, there is in-vitro synergy between clofazimine and amikacin for *M simiae* isolates.[11] In addition, variable proportions of clinical strains can be susceptible to moxifloxacin (and to ciprofloxacin, to a lesser extent), aminoglycosides, and cycloserine.[125,127]

A systematic literature review by two independent experts identified 11 case reports and case series describing 197 patients with *M simiae* pulmonary disease in the scientific literature published in English, but no evidence-based management recommendations for *M simiae* pulmonary disease based on clinical trial

data.[116,117,121,122,128-134] The largest study of 102 patients was from Israel; no treatment failures or relapses were reported during a mean follow-up of 24 months, with patients receiving clarithromycin, ethambutol, and rifampicin treatment for at least 12 months.[121] Although the 1997 ATS criteria were reportedly used to select patients, 38 (37%) of 102 patients were asymptomatic and had an unremarkable chest radiograph; therefore, not fulfilling these criteria. The expert panel concluded that data from this study could not be considered reliable enough to form a basis for treatment recommendations.[121]

The treatment regimen for *M simiae* pulmonary disease includes at least three drugs: azithromycin (250–500 mg) once a day or clarithromycin (500 mg) twice a day, moxifloxacin (400 mg) once a day, co-trimoxazole (trimethoprim 800 mg and sulfamethoxazole 160 mg) twice a day, amikacin (15–20 mg/kg) intravenously once a day or amikacin (15–25 mg/kg) three times a week (lower in older patients and with prolonged use), or clofazimine (100–200 mg) once a day. Depending on antimycobacterial drug susceptibiltity testing, accepted treatment regimes could be a clofazimine, amikacin, and azithromycin combination or a azithromycin, moxifloxacin, and co-trimoxazole combination,[3,16] or a azithromycin and moxifloxacin combination with one or two additional drugs based on antimycobacterial drug susceptibility testing results; clofazimine and aminoglycosides would be the most appropriate options.[125] Surgical resection of affected lobes should be evaluated as an adjunctive treatment option.[16] Optimal treatment duration is unknown; experts consider treating for at least 12 months after conversion to negative sputum culture, possibly introducing a step-down approach to consolidation therapy (eg, stop intravenous amikacin) once clinical, microbiological, and radiological improvement has been documented.

M szulgai

M szulgai is an unusual cause of pulmonary disease and accounts for less than 1% of human respiratory isolates of NTM; however, the isolation of *M szulgai* appears to be clinically relevant in most cases.[135–137] Isolates are usually susceptible in vitro to clarithromycin and rifampicin. The largest case series reporting on antimycobacterial susceptibility testing of *M szulgai* included 23 strains of *M szulgai*.[106] Drug resistance was observed in all 23 (100%) strains to isoniazid, in 9% of strains to ethambutol, in 26% of strains to ciprofloxacin, 13% of strains to amikacin, and in 4% of strains to rifampicin. All 23 strains of *M szulgai* were susceptible to clarithromycin. In-vitro data suggest susceptibility to clofazimine (appendix p 2). Later generation fluoroquinolones were not tested.

A systematic literature review conducted by two independent experts identified 25 retrospective case reports and case series, including a total of 44 patients with *M szulgai* pulmonary disease described in the scientific literature published in English[136,138–149] but no evidence-based management recommendations for *M szulgai* pulmonary disease based on clinical trial data. Most patients were treated with a combination of rifampicin, ethambutol, and clarithromycin or azithromycin. Other treatments included a mixture of rifampicin-based regimens; usually a combination of rifampicin with two or more drugs: isoniazid, ethambutol, fluoroquinolones, ethionamide, and intravenous drugs. Treatment duration was variable; 12 months was most frequently used (range 5–18 months). The outcome was favourable in 85% of patients treated with rifampicin, clarithromycin, and azithromycin combination regimens; no relapses were observed among the five (11%) patients that post-treatment follow-up was available for. The cure rate was 81% among 21 patients treated with clarithromycin and azithromycin sparing regimens; unfavourable outcomes included one failure of treatment after 6 months and one relapse related to non-compliance. Four (9%) patients underwent surgery, but it was only performed to treat *M szulgai* pulmonary disease in two of these patients, and one of these two patients had a tissue culture sample that was negative for *M szulgai*.

Treatment for *M szulgai* pulmonary disease should include at least three drugs that the organism shows in-vitro susceptibility for. Based on the low level evidence available, a combination of rifampicin (600 mg) once a day, azithromycin (250–500 mg) once a day or clarithromycin (500 mg) twice a day, and ethambutol (15 mg/kg) once a day for 12 months is recommended. Clofazimine (100–200 mg) once a day can be used if there is intolerance or drug resistance to macrolides, rifamycins, or ethambutol. Intravenously administered drugs (eg, amikacin) are alternatives in case of intolerance or resistance to the recommended orally available drugs. There are no in-vitro susceptibility data or clinical experience with later-generation fluoroquinolones. In such cases, if a treatment with a macrolide, rifamycin, and ethambutol cannot be used, it is advised to prolong treatment to 12 months after conversion to culture negative. There is no evidence to recommend surgery as part of the treatment for *M szulgai* pulmonary disease.

A summary of slowly growing NTM treatment recommendations is shown in table 3.

Conclusion

We did a systematic review of the literature and consensus process to provide treatment recommendations for pulmonary diseases caused by seven additional NTM not covered in the recent ATS, ERS, ESCMID, and IDSA or BTS clinical practice guidelines.[1,2,4]

With the exception of *M malmoense*, where recommendations are based on two randomised controlled trials and three retrospective cohort studies, the consensus recommendations by the panel members for the other six NTM species are based on case reports and case series only, thus are graded to be very low level evidence. Higher level evidence from patient registries

and clinical trials to determine the best treatments for patients affected by pulmonary diseases caused by the other six NTM species are needed to inform clinicians in the future about the best management options for their patients.

Contributors

CL, CLD, and EC developed the idea and outline for the manuscript. SLK performed the electronic systematic literature searches. All co-authors contributed equally to the hand-search of the selected literature, the consensus process, drafting of the manuscript, and manuscript revision.

Declaration of interests

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