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Review article

Non-tuberculous mycobacteria disease pre-lung transplantation: A systematic review of the treatment regimens and duration pre- and post-transplant.

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ABSTRACT

Background: There is lack of consensus on non-tuberculous mycobacteria pulmonary disease (NTM-PD) treatment regimen and duration in patient listed for lung transplantation (LTx). We conducted a systematic review on treatment regimen and duration pre- and directly post-LTx, for patients with known NTM-PD pre-LTx. Additionally, we searched for risk factors for NTM disease development post-LTx and for mortality.

Methods: Literature was reviewed on PubMed, Embase and the Cochrane Library, for articles published from inception to January 2022. Individual patient data were sought.

Results: Sixteen studies were included reporting 92 patients. Most frequent used agents were aminoglycosides and macrolides for *Mycobacterium abscessus* (*M. abscessus*) and macrolides and tuberculostatic agents for *Mycobacterium avium* complex (*M. avium* complex). The median treatment duration pre-LTx was 10 months (IQR 6–17) and 2 months (IQR 2–8) directly post-LTx. Longer treatment duration pre-LTx was observed in children and in patients with *M. abscessus*. 46% of the patients with NTM-PD pre-LTx developed NTM disease post-LTx, related mortality rate was 10%. Longer treatment duration pre-LTx ($p < 0.001$) and sputum non-conversion pre-LTx ($p = 0.003$) were significantly associated with development of NTM-disease post-LTx. Longer treatment duration pre-LTx ($p = 0.004$), younger age ($p < 0.001$) and sputum non-conversion ($p = 0.044$) were risk factors for NTM related death.

Conclusions: The median treatment duration pre-LTx was 10 months (IQR 6–17) and 2 months (IQR 2–8) directly post-LTx. Patients with longer treatment duration for NTM-PD pre-LTx and with sputum non-conversion are at risk for NTM disease post-LTx and for NTM-related death. Children were particularly at risk for NTM related death.

1. Introduction

Lung transplantation (LTx) is a treatment option for selected patients with life-threatening, advanced lung disease, unresponsive to other medical or surgical treatments. Non-tuberculous mycobacteria (NTM) are frequently isolated from the diseased airways of patients listed for

Abbreviations: AZA, azathioprine; CF, Cystic Fibrosis; CLAD, chronic lung allograft dysfuncion; COPD, chronic obstructive pulmonary disease; CYC, cyclosporine; IPD, individual patient data; LTx, lung transplantation; MMAT, mixed methods appraisal tool; MMF, mycophenolate mofetil; MTOR inhibitor, mammalian target of rapamycin inhibitor; NTM, non-tuberculous mycobacteria; NTM-PD, non-tuberculous mycobacteria pulmonary disease.

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LTx with structural lung disease, such as cystic fibrosis (CF) [1–3].

NTM pulmonary disease (NTM-PD) is defined as symptomatic patients with HRCT compatible with NTM disease and positive sputum cultures, bronchial washes or biopsies and exclusion of other causes [4]. NTM-PD pre-LTx, may lead to post-LTx NTM disease (pulmonary or disseminated disease), due to spillage of native lung contents into the pleural cavity and surgical wounds, or reinfection from spread from infected airways above the anastomoses.

NTM-PD used to be a contra-indication for LTx. However, several small studies have shown that LTx is feasible [5–9]. Currently, according to ISHLT 2021 guidelines, patients with NTM-PD may be referred for LTx, but should be managed at centers with expertise and protocols for NTM-PD [10].

NTM, especially *Mycobacterium abscessus* (*M. abscessus*) and *Mycobacterium avium* complex (*M. avium* complex), are associated with increased post-LTx mortality and the development of chronic lung allograft dysfunction (CLAD) [11,12]. To reduce the risk of post-LTx NTM disease, patients listed for LTx, should be treated pre-LTx to eradicate the NTM or, at least to reduce mycobacterial burden [13]. In general, NTM-PD is hard to treat. Cure rates for NTM are variable, for *M. avium* complex 42–67% and for *M. abscessus* 16–65% [14–16]. Directly after LTx, NTM treatment might be necessary to prevent transition from NTM-PD pre-LTx to pulmonary or disseminated NTM disease post-LTx, in the immunocompromised patient. Although treatment targeting therapy for most NTM species are standardized worldwide, there is a lack of consensus on treatment options, strategies and duration in patient listed for LTx [15]. Post-LTx, drug interactions between antimycobacterial agents and immunosuppressive therapy (especially calcineurin- and mammalian target of rapamycin (mTOR)-inhibitors) are challenging and may lead to severe side effects, which are the result of high drug blood concentrations due to drug-drug interactions, poor kidney function and high doses necessary for efficacy. This may lead to poor NTM therapy tolerability, affecting duration and effectiveness of treatment.

The primary aim of this review is to describe the different treatment regimens and duration pre- and directly post-LTx and to evaluate the effect of treatment duration on development of NTM post-LTx and on mortality. Secondary aims were to describe additional risk factors for NTM disease development post-LTx and for mortality.

2. Methods

The review protocol was registered in PROSPERO (CRD42022329301). The Preferred Reporting Items for Systematic Review (PRISMA) guidelines were followed in reporting of this review [17]. The literature search, was conducted on major databases including PubMed, EMBASE and Cochrane Library. The original search query is shown in supplement 1. References of the included papers were reviewed for missing articles. First, the titles and abstracts of search results were screened independently by two authors, thereafter the full texts were evaluated for inclusion by J.G. and S.R. Discrepancies were solved by consensus or by consulting a third author (O.A.). (supplement 2) Studies were eligible if they investigated LTx patients (adults and children), with NTM-PD pre-LTx and treated with oral, nebulized or intravenous antibiotics pre- and/or directly post-LTx. Directly post-LTx treatment was defined as treatment started directly post-LTx for pre-LTx NTM-PD, which might be continuation of the pre-LTx treatment (supplement 3). Studies were excluded when investigating: 1) only post-LTx NTM disease, 2) data from animal studies or NTM isolated from explanted lungs, 3) *Mycobacterium tuberculosis*.

2.1. Data extraction

The following data were extracted from each included study using a standardized data extraction form: authors, publication date, design, objective, follow-up, patient characteristics, NTM species pre-LTx, treatment regimens pre-LTx and directly post-LTx, treatment duration, frequency of NTM disease post-LTx, mortality, graft loss during follow-up. When needed authors were contacted to add information. Papers without original data, conference abstracts, studies with duplicate data, and review papers were excluded.

2.2. Risk of bias (quality) assessment

The mixed methods appraisal tool (MMAT) is used to assess risk of bias of the papers [18]. Two reviewers were independently involved in the appraisal process (J.G. and S.R.). Discrepancies were resolved by consensus or by consulting a third author (O.A).

2.3. Outcomes

Study outcome measures in patients with pre-LTX NTM-PD included the development of post-LTX NTM disease and mortality.

2.4. Statistical analysis

All analyses were performed using SPSS (23.0; SPSS Inc., Chicago, Illinois, USA) for Mac. Variables are expressed as median (quartiles). Mann–Whitney *U* test and chi-squared test were used to compare parameters between patients who developed NTM disease post-LTx and those without development of NTM disease post-LTx. Furthermore, parameters were compared between patients who survived and died due to NTM disease. A Cox proportional hazards model with time dependency was used to compare post-LTx survival between patients with and without post-LTx NTM-PD. A p-value of <0.05 was considered significant.

3. Results

3.1. Search results, study description and quality

Sixteen studies were included providing data on 92 cases in total (PRISMA flowchart supplement 2) [9,19–33]. Four of the original studies had a case-control design, 6 were cohort studies, 5 were case series/reports and 1 was a survey study (supplement 4). All studies had a retrospective design. Authors of 2 studies provided additional data after being contacted.

Study quality regarding NTM-PD treatment varied and was mostly hampered by small sample size, the lack of appropriate measurements and incomplete outcome data (MMAT results in supplement 5).

3.2. Patients with NTM-PD

Patient characteristics of the 92 patients are summarized in Table 1. The median age was 24 (IQR 18–32) years, 18 (20%) were children (age $<$ 18 year) and 57 (57%) were female. The most frequent indications for LTx were cystic fibrosis (CF) (75/92; 82%), followed by pulmonary fibrosis (6/92; 8%), and COPD/, Alpha-1 antitrypsin deficiency (6/92; 8%). Immunosuppressive therapy was described in 11 studies. Sixty percent of the patients received induction therapy. Patients received triple maintenance immunosuppression therapy in all but one study, and consisted mainly of tacrolimus (TAC)/cyclosporine (CYC), mycophenolate mofetil (MMF)/azathioprine (AZA)and prednisolone.

3.3. NTM-PD treatment and treatment duration

Treatment data were available for 76 patients pre-LTx and for 54 patients directly post-LTx. Eighteen out of 76 (24%) patients did not receive treatment pre-LTx and 5 out of 54 patients (9%) directly post-LTx. Of the 18 patients who did not receive treatment pre-LTx, 15 were considered not to have met criteria for NTM-PD, 1 patient spontaneously cleared the *M. abscessus* pre-LTx and for 2 patients the reason

Table 1
Clinical Features of patients with NTM-PD pre-LTx who developed NTM disease post-LTx and/or died due to NTM disease.

Variable	All patients $n = 92$	NTM post-LTx $n = 42$	*p*-value	NTM death $n = 9$	*p*-value
Age					
<18 years, n (%)	18	12 (67)	0.052	6 (33)	<
> 18 years, n (%)	66	27 (41)		3 (5)	0.001
Gender					
Male, n (%)	32	16 (50)	0.607	4 (13)	0.678
Female, n (%)	52	23 (44)		5 (10)	
Transplant indication, n (%)			0.682		0.664
Cystic Fibrosis	75	34 (45)		8 (11)	
COPD/AATD	6	4 (67)		0 (0)	
Fibrosis	6	2 (33)		1 (17)	
Other	5	2 (40)		0 (0)	
NTM species, n (%)					
M. abscessus	68	34 (50)	0.237	8 (12)	0.517
M. avium complex	18	7 (39)		1 (6)	
other	6	1 (17)		0 (0)	
Sputum conversion, n (%)			0.003		0.044
Yes	22	5 (23)		0 (0)	
No	49	30 (61)		8 (16)	

for withholding treatment is unknown. The 5 patients who did not receive treatment directly post-LTx, had not met diagnostic criteria for NTM-PD according to the authors. In 78% patients with NTM-PD pre-LTx and in 94% directly post-LTx medication was delivered intravenously.

The median treatment duration pre-LTx was 10 months (IQR 6–17) in 14 studies (64 patients). The mean treatment duration directly post-LTx was 2 months (IQR 2–8) in 12 studies (51 patients). The effect of treatment duration and thorax irrigation on the development of NTM disease post LTx and on NTM related mortality is shown in Table 2. Longer treatment duration pre-LTx was significantly associated with the development of NTM disease post-LTx ($p < 0.001$) and with NTM related mortality ($p = 0.004$). Treatment duration directly post-LTx was not associated with the development of NTM disease ($p = 0.374$) or NTM related mortality ($p = 0.105$). In 22 long term survivors (> 5 year post-LTx) treatment duration pre-LTx was 7 months (IQR 6–12) and post-LTx 2 months (IQR 2–3). There was an association between *M. abscessus* and age with treatment duration: patients with *M. abscessus* and children, had significant longer treatment duration pre-LTx ($p < 0.001$ for both).

In 10 studies (70 patients) information about surgical procedures to reduce NTM load at the time of LTx was available. Pleural cavity irrigation with or without lymphadenectomy was performed in 32 patients (35%). Pleural cavity irrigation had no significant effect on the development of NTM disease post-LTx or on mortality (Table 2).

Table 2
Effect of treatment duration and thorax irrigation on the development of NTM disease post LTx and on NTM related mortality.

Variable	NTM post-LTx n = 42	No NTM post-LTx $n = 50$	*p*-value	NTM death n = 9	Survived/ non-NTM death $n = 83$	*p*-value
Treatment duration						
Pre-LTx, months	12 (8–36)	6 (3–12)	< 0.001	30 (18–60)	7 (6–12)	0.004
Post-LTx, months	3 (2–12)	2 (2–6)	0.374	2 (1–2)	2 (2–8)	0.105
Thorax irrigation	18	14	0.064	5	27	0.311

NTM, Non-tuberculous mycobacteria; LTx, lung transplant.

3.4. *M. abscessus* disease and treatment

Supplement 6 shows all the NTM species identified in this review. Combining all 16 studies the most common isolated NTM species was *M. abscessus*. Pre-LTx 68 patients (74%) had *M. abscessus* NTM-PD. Of those, there was 1 patient with subspecies *bolletii*, 5 patients with subspecies *massiliense* and 7 patients with subspecies *abscessus*. In 55 patients the *M. abscessus* subspecies was not available. *M. avium* complex was isolated in 20% of the patients, *M. fortuitum* in 4%, in one patient both *M. abscessus* and *M. avium* complex were isolated and in one patients the NTM species was not specified (supplement 6).

M. abscessus treatment data were available in 60 patients pre-LTX and 58 patients directly post-LTx. The most frequently used agents pre- and directly post-LTx for *M. abscessus* are shown in Fig. 1a. The most frequent used classes of antibacterial agents used for *M. abscessus* pre-LTx and directly post LTx were aminoglycosides and macrolides (Table 3a). Treatment regimens for *M. abscessus* included a combination of 3 different agents pre-Ltx (IQR 3–4) and 3 (IQR 2–5) post-LTx. The median treatment duration for *M. abscessus* pre-LTx was 12 (IQR 6–20) months and directly post-LTx 2 (IQR 2–8) months. Treatment duration pre-LTx was significant longer in patients with *M. abscessus* than in patients with other NTM species ($p < 0.001$). The sputum conversion rate after pre-LTx treatment in patients with *M. abscessus* was 34%. In patients with *M. abscessus* pre-LTx 34 (50%) developed NTM disease post-LTx (Table 1) and 8 (12%) died due to NTM disease. Of the 9 patients who died due to NTM disease, 8 patients had *M. abscessus* pre-LTx ($p = 0.517$).

3.5. *M. avium* complex disease and treatment

Pre-LTx 18 patients (20%) had *M. avium* complex NTM-PD. *M. avium* complex treatment data were available in 15 patients pre-LTX and 16 patients directly post-LTx. The most frequently used agents pre- and directly post-LTx for *M. avium* complex are shown in Fig. 1b. The most frequent used classes of antibacterial agents used for *M. avium* complex pre-LTx and directly post LTx were macrolides and tuberculostatic agents (Table 3b). Treatment regimens pre-LTx and post-LTx for *M. avium* complex included a combination of 3 different agents (IQR 0–3). The median treatment duration for *M. avium* complex pre-LTx was 6 months (IQR 3–7) and directly post-LTx 3 months (IQR 1–10). The sputum conversion rate after pre-LTx treatment in patients with *M. avium* complex was 25% pre-LTx. In patients with *M. avium* complex pre-LTx 7 (39%) developed NTM disease post-LTx (Table 1a) and 1 (6%) died due to NTM disease. Of the 9 patients who died due to NTM disease, 1 patient had pre-LTx. There was no difference in the risk of NTM disease post-LTx or mortality between patients with *M. avium* complex, *M. abscessus* or other species (Table 1).

3.6. Development of NTM disease post-LTX and risk factors

In the 92 patients with pre-LTx NTM-PD, 42 (46%) patients developed NTM disease post-LTx (Table 1). The median time from LTx to NTM disease post-LTx was 2 (IQR 1–9) months. Eleven (26%) of the patients with NTM disease post-LTx had disseminated disease, 20 (48%) had pulmonary disease, 7 (17%) had surgical wound infection, 2 (5%) had both lung and surgical wound infection, 1 patient had a breast abscess and 1 patient had osteomyelitis. Nine patients (21%) with NTM disease post LTx died. The NTM species pre-LTx were the same as post-LTx, in all but one.

Clinical features of patients with NTM-PD pre-LTx who developed NTM disease post-LTx are shown in Table 1. Twelve of the 18 children (67%) developed NTM disease post-LTx, whereas 27 of the 66 adults (41%) developed NTM disease post-LTx ($p = 0{,}052$). The risk of NTM disease post-LTx was significant higher in patients without sputum conversion than in patients with sputum conversion pre-LTx (61% vs 23%, $p = 0.003$).

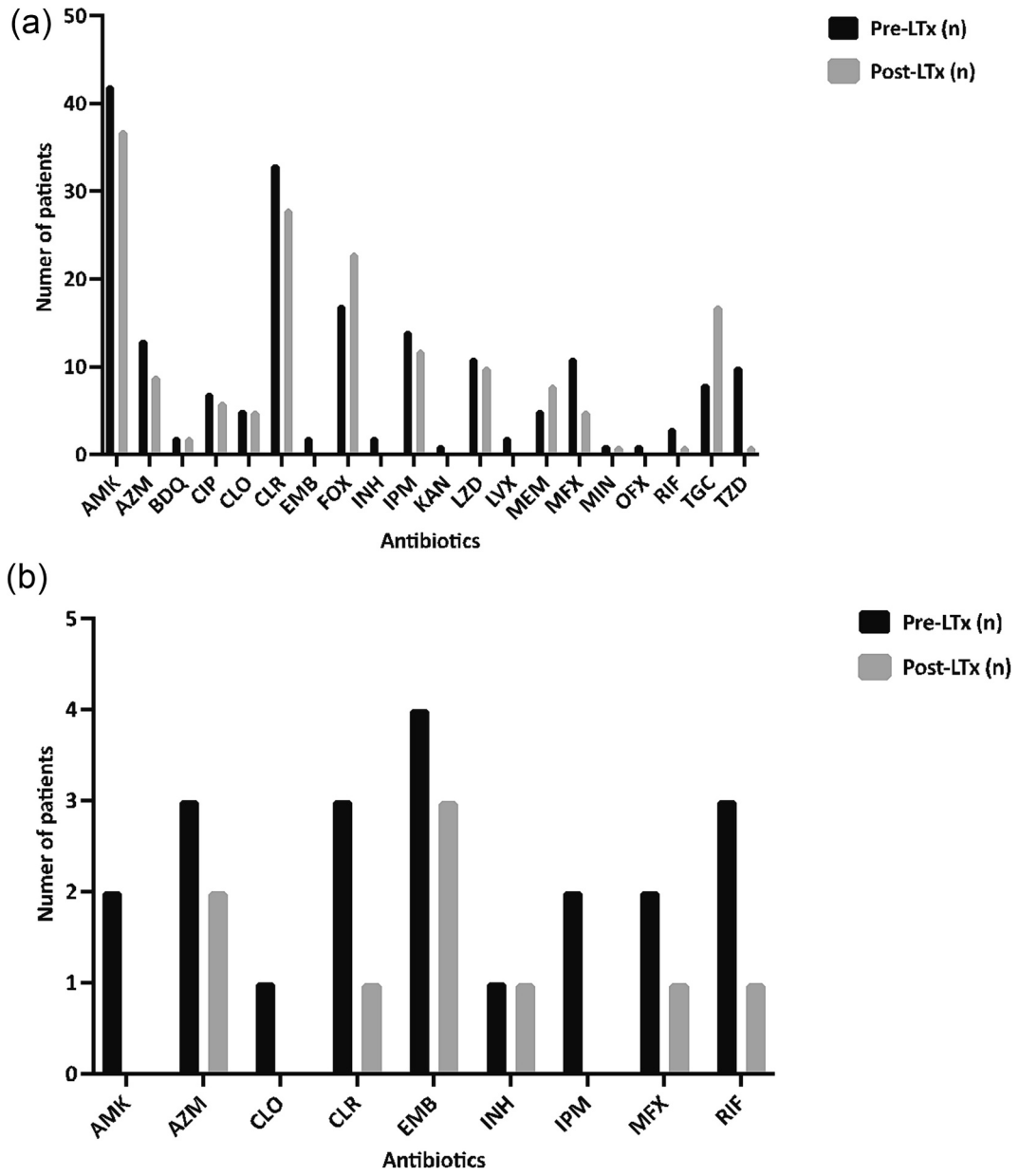

Fig. 1. a. Treatment for *M. abscessus* pre- and post-LTx.
b. Treatent for *M. avium* complex pre- and post-LTx.
LTx, lung transplantation; AMK: amikacin; AZM: azithromycin; BDQ: bedaquiline; CIP: ciprofloxacin; CLO: clofazimine; CLR: clarithromycin; EMB: ethambutol; FOX, cefoxitin; INH: isoniazid; IPM: imipenem; KAN: kanamycin; LZD: linezolid; LVX: levofloxacin; MEM: meropenem; MFX: moxifloxacin; MIN: minocycline; OFX: ofloxacin; RIF: rifampin; TGC: tigecycline; TZD: tedizolid.

Table 3a
Class of antibacterial agents used for *M. abscessus* pre-LTx and post LTx.

Antibiotic class	Pre-LTx	Post-LTx
	Patients n (%)	Patients n (%)
Aminoglycosides	42 (70)	37 (64)
Cephalosporins	20 (33)	26 (45)
Tuberculostatic agents	8 (13)	3 (5)
Fluoroquinolones	20 (33)	10(17)
Macrolides	47 (78)	37 (64)
Tetracyclines	13 (22)	17 (29)
Carbapenems	19 (32)	19 (33)
Oxazolidinones	20 (33)	11 (19)
Clofazimine	5 (8)	5 (9)

LTx, lung transplant; NTM, Non-tuberculous mycobacteria.

Table 3b
Class of antibacterial agents used for *M. avium* complex pre-LTx and post LTx.

Antibiotic class	Pre-LTx	Post-LTx
	Patients n (%)	Patients n (%)
Aminoglycosides	2 (13)	0 (0)
Tuberculostatic agents	4 (27)	3 (19)
Fluoroquinolones	2 (13)	1 (6)
Macrolides	6 (40)	3 (19)
Carbapenems	2 (13)	0 (0)
Clofazimine	1 (7)	0 (0)

LTx, lung transplant; NTM, Non-tuberculous mycobacteria.

3.7. Survival and risk factors for NTM related death

Forty-four (48%) patients survived till follow-up, 9 (10%) patients died due to NTM disease and 39 (42%) died, not-NTM related within 97 months. Median follow up time in patients who survived was 53 (IQR 24–95) months. The median survival time from LTx to NTM related death was 3 (IQR 2–16) months, and 22 (IQR 5–52) months for non-NTM related death.

In patients who died due to NTM disease, the median time between the first positive NTM culture and LTx was 4 (IQR 2–7) year. Moreover, these patients were very young when NTM were cultured for the first time pre-LTx: median age 11 (IQR 4–13) year.

Characteristics of patients who died due to NTM disease are presented in Table 1. In children the NTM related mortality was significant higher than in adults (6/18 (33%) vs 3/66 (5%); $p < 0.001$). Seventeen out of 18 children had *M. abscessus* NTM-PD (94%; $p = 0.100$). The risk of NTM related death was significant higher in patients without sputum conversion than in patients with sputum conversion pre-LTx (8/49 (16%) vs 0/22 (0%), $p = 0{,}044$). Notably, there was an association between sputum conversion and age: sputum conversion was achieved pre-LTx in less children compared to adults (2/7 (28%) vs 26/46 (56%), $p = 0.019$).

In 83 patients the time to follow up or to death was available. The median survival time for patients with NTM disease post-LTx was 48 months and for patients without 62 months. The 6 month survival rate in patient with NTM disease post-LTx was 79% and for patients without NTM disease post-LTx 85%. Survival rates at 1 year were 70% for patients with NTM disease post-LTx and 80% for those without. There was no significant difference in survival between patients with or without NTM disease post-LTx (Table 4; $p = 0.103$). In the 22 long-term survivors (> 5 year), 77% had *M. abscessus* NTM-PD pre-LTx, 27% had NTM disease post-LTx and in 32% sputum conversion was achieved pre-LTx. The overall 30 day survival rate in these 83 patients was 96% and the overall 5-year survival rate was 48%.

3.8. Chronic lung allograft dysfunction

In 71 (77%) patients data about CLAD were available. Seventeen (18%) patients with pre-LTX NTM-PD developed CLAD post-LTX. There was no significant association between CLAD and NTM disease post-LTX: 28% of the patients with NTM disease post-LTx developed CLAD, whereas 21% of patients without NTM disease post-LTX developed CLAD ($p = 0.550$).

4. Discussion

In this systematic review treatment regimens and duration pre-LTx and directly post-LTx in patients with pre-LTx NTM-PD are described. We showed that longer treatment duration pre-LTx was significantly associated with the development of NTM disease post-LTx and with NTM related mortality.

In patients who meet the diagnostic criteria for NTM-PD, initiation of treatment rather than watchful waiting is suggested. In patients with *M. abscessus* disease, a multidrug regimen that includes at least three active agents (guided by in vitro susceptibility) is recommended [4]. Not all patients in this review received treatment, because these patients did not met the criteria for NTM-PD and colonization was suggested. However, the concept of NTM airway colonization has never been studies rigorously and it is generally assumed that colonization is, in fact, indolent or slowly progressive disease [34].

The most frequently used agents for *M. abscessus* were macrolides and aminoglycosides, and for *M. avium* complex macrolides and ethambutol, which is according to the guidelines [4]. The median treatment duration for *M. abscessus* was 12 (IQR 6–20) months pre-LTx and 2 (IQR 2–8) months directly post-LTx. For *M. avium* complex the median treatment duration was 6 (IQR 3–7) months pre-LTx and 3 months (IQR 1–10) directly post-LTx. The optimal duration of therapy for *M. abscessus* and *M. avium* complex disease is not currently known, nevertheless treatment for at least 12 months after culture conversion is recommended for *M. avium* complex [4]. Drug intolerance and drug interactions complicates the optimal duration of therapy. Clinicians might prefer to initiate long-time aggressive treatment pre-LTx, because most patients are not immunocompromised pre-LTx and there is no need to take into account drug interactions with immunosuppressive agents. However, given the long time on waiting list for LTx with severe lung disease, a vulnerable state and co-infection with other bacteria or fungus, make long treatments for NTM very challenging. Moreover, waiting time for LTx varies and makes it difficult to plan therapy for a defined time until surgery. Therefore, in the difficult setting of pre- and post-LTx NTM-PD, management should be restricted to expert centers [4].

We showed that longer treatment duration pre-LTx was associated with higher NTM disease rates post-LTx and NTM-related mortality. However, treatment duration itself, is affected by two other variables: age and *M. abscessus* disease. In younger patients and patients with *M. abscessus* NTM-PD treatment duration pre-LTx was longer. In addition, it might be that patients, with *M. abscessus* disease and younger age, needed longer treatment because of more severe NTM disease or more extensive structural lung damage and therefore were at risk for NTM disease post-LTx. Unfortunately, information about the severity of NTM disease and the extensiveness of the pre-LTx NTM-PD treatment was not available. What we do know, is that patients with NTM disease post-LTx who died, had NTM-PD long before LTx at very young age. Most of these patients had oral and IV regiments, but information about the duration of oral versus IV treatment is missing. Longer treatment duration pre-LTx did not result in a higher sputum conversion rates, which is comparable with the results of the Dutch CF foundation [35]. Zomer et al. showed that in CF patients with NTM-PD the sputum conversion rate was 50% after 1 year of treatment, which did not change after prolongation of treatment (> 1 year) [35].

In this review, the rate of NTM disease post-LTx after prior pre-LTx NTM-PD is high (46%), which underlines the need to sustain treatment rather than discontinue it directly post-LTx. However, the heterogeneity of the used agents, variable duration of treatment pre- and directly post-LTx and the unknown drug susceptibility preclude any firm recommendation regarding treatment of pre-LTx NTM-PD.

Our secondary aim was to describe additional risk factors for NTM disease development post-LTx and for mortality. Patients without sputum conversion pre-LTx did develop NTM disease post-LTx more often than patients with sputum conversion. Therefore, it is a good goal to aim for sputum conversion before LTx [36]. If sputum conversion fails, it is advisable to start NTM treatment immediately post-operatively to prevent NTM disease post-LTx.

Importantly, we showed that children are at greater risk for NTM related death than adults. Most children (94%) in this review had *M. abscessus* NTM-PD. Catherinot et al. showed that the clinical presentation of NTM-PD due to *M. abscessus* is usually more severe, and the affected patients are younger with more severe CF [37]. Furthermore, Zomer at al showed that children with CF and NTM-PD had more severe pulmonary function decline than adults with CF and NTM-PD [35]. In children treatment duration pre-LTx was significantly longer than for adults. Treatment duration pre-LTx in children might be longer because these children more often had *M. abscessus* NTM-PD (94% of the

Table 4
Survival in LTx patients, with and without NTM-PD post-LTx.

NTM-PD after LTx	Survival	
	Alive	Death
No, n (%)	23 (46)	27 (54)
Yes, n (%)	21 (50)	21 (50)

LTx, lung transplantation; NTM-PD, non-tuberculous mycobacteria pulmonary disease.

children). Moreover, these children had first NTM isolation long before transplant, with longer treatment duration, probably due to eradication failure, which might have resulted in worse outcome. NTM treatment in children is challenging. Saint et al. retrospectively collected data from children with CF without LTx from 11 CF specialist centres. They reported refractory disease in 20% after treatment, drug cessation due to adverse events in 30%, and dose change in 10% [38].

M. abscessus NTM-PD was not a direct risk factor for NTM disease post-LTx or NTM related death. However 94% of the children, who were at greater risk for NTM disease post-LTX and NTM related death, had *M. abscessus* NTM-PD. In non-LTx studies a poor prognosis is found for *M. abscessus* NTM-PD and *M. abscessus* is considered a clinically problematic pathogen which is extremely difficult to eradicate given its naturally multidrug resistant properties. [21,22,27,39,40]. However, our results show that not only the aetiological NTM species, but the duration of the treatment and host factors such as age are prognostic factors for NTM disease and mortality post-LTx. Besides, the duration of the treatment depends on the bacterial load of the NTM-PD, which might be reflected by the lack of sputum conversion [41].

This review has some limitations. The literature available for this review consists of small non-randomized case-series and cohort studies with important differences in quality of evidence, methods, sample size and follow-up time. Despite the limited data, we managed to find 92 patients for whom individual patient data were provided in 16 studies.

5. Conclusions

Median treatment duration pre-LTx was 10 months (IQR 6–17) and directly post-LTx 2 months (IQR 2–8). Treatment regimens for *M. abscessus* included a combination of 3 different agents and most frequent used agents were aminoglycosides and macrolides. Treatment regimens for *M. avium* complex included a combination of 3 different agents and most frequent used agents were macrolides and tuberculostatic agents. Longer treatment duration pre-LTx was observed in children and in patients with *M. abscessus* NTM-PD and was significantly associated with the development of NTM disease post-LTx and with NTM related mortality. Patients without sputum conversion pre-LTx had a higher risk of NTM disease post-LTx and NTM related mortality. Children were particularly at risk for NTM related death.

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Table 1. NTM -PD, non-tuberculous mycobacteria pulmonary disease; LTx, lung transplant; NTM, Non-tuberculous mycobacteria; COPD, chronic obstructive pulmonary disease; AATD, alpha-1 antitrypsin defiency;

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.trre.2023.100800.

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