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Non-tuberculous mycobacterial infections in solid organ transplant recipients: An update

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ABSTRACT

Non-tuberculous mycobacteria are ubiquitous environmental organisms that are now increasingly recognized as important causes of clinical disease in solid organ transplant recipients. Risk factors of non-tuberculous mycobacteria infection are severe immunologic defects and structural abnormalities. Lung transplant recipients are at higher risk for non-tuberculous mycobacterial disease compared to recipients of other solid organs. The clinical presentation could be skin and soft tissue infection, osteoarticular disease, pleuropulmonary infection, bloodstream (including catheter-associated) infection, lymphadenitis, and disseminated or multi-organ disease. Management of non-tuberculous mycobacteria infection is complex due to the prolonged treatment course with multi-drug regimens that are anticipated to interact with immunosuppressive medications. This review article provides an update on infections due to non-tuberculous mycobacteria after solid organ transplantation, and discusses the epidemiology, risk factors, clinical presentation, and management.

1. Introduction

Non-tuberculous mycobacteria (NTM) consist of over 140 distinct species of ubiquitous environmental organisms that are often found in soil and water. NTMs are generally considered uncommon causes of clinical disease in the general population. However, NTM disease appears to be increasingly reported. In a population-based epidemiologic study in the United States, the incidence of skin and soft tissue disease due to NTM increased from 0.7 per 100,000 population during 1980–1999 to 2.0 per 100,000 population during 2000–2009 [1]. NTM infections after solid organ transplantation (SOT) are also perceived to have increased in frequency in recent years, reflecting increased exposure, increased length of survival, and improved methods for diagnosis [2]. Among all SOT populations, lung transplant recipients are at higher risk for NTM disease for several possible reasons, such as the direct exposure of the transplanted lung to the environment, and structural abnormalities in lung transplant recipients may interfere with host defenses against inhaled organisms. The increased risk of NTM disease in these patients may also be a reflection of the severity of immunologic deficiencies, given that lung transplantation is associated with a more intense degree of immune suppression than other types of organ transplantation [3].

Although relatively rare in incidence compared to other post-transplant infections, recognizing diseases due to NTM is important, as delays in diagnosis may lead to poor outcomes. Management of these NTM infections is also frequently complex due to the prolonged treatment course and the anticipated drug–drug interactions between antimycobacterial drugs and the immunosuppressive medications.

This review article will provide an update on the literature of NTM infections after SOT, and discuss the epidemiology, risk factors, clinical presentation, and management in the context of organ transplantation.

2. Epidemiology

The epidemiology of NTM infections in SOT recipients is not fully defined. Its incidence is difficult to determine with certainty as reporting of disease is not mandatory, and the ubiquitous nature of these organisms makes it hard to determine whether or not NTM species isolated from non-sterile source are clinically relevant. *Conservation studies have isolated NTM from both natural and potable water sources [4]–[7]. For example, Mycobacterium xenopi and M. kansasii are common in man-made water systems while M. marinum is linked to aquatic environments and is often called "fish*

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tank granuloma" [8],[9]. Often, the differentiation between colonization and clinical disease is difficult.

There is also evidence to suggest that nosocomial transmission of NTM is increasing, and results in conditions ranging from harmless colonization to invasive infection. These hospital-borne infections are usually more common among patients undergoing surgery, those on hemodialysis, or have immune suppressed conditions [5]. To date, only a few cases have been reported among SOT recipients [10].

The epidemiology among transplant recipients varies widely based on geography and type of transplantation [11]. Hence, the incidence can only be estimated based on available case series and anecdotal reports. Among renal transplant recipients, the estimated incidence of NTM infections is between 0.16% and 0.55% [12–20]. Slightly higher incidence rates are reported in heart transplant recipients (2.8%) [21] and lung transplant recipients (0.46 to 4.4%) [22–25]. For some unclear reason, NTM infections among liver transplant recipients have not been systematically reported, but the estimated incidence rate is comparatively low at 0.04% [15]. *We have found no reported cases of NTM infections among small bowel, composite tissue, and pancreatic transplants.*

The frequency and types of specific NTM infections, and the causative species varies by the type of organ transplant. To date, there have been more than 20 different species reported to cause disease in transplant recipients. Interestingly, *Mycobacterium kansasii* is the most commonly reported NTM among heart transplants [2]. Rapidly growing mycobacteria (RGM) are reported less frequently among SOT recipients than hematopoietic stem cell transplants (HSCT) recipients. Among SOT recipients with NTM infection, RGM were reported in approximately 40% of renal transplants and 10% of heart and lung transplant recipients [11].

3. Risk factors

Among the risk factors that have been associated with NTM disease, in general, include immunocompromised states (such as acquired immunodeficiency syndrome), treatment with monoclonal antibody therapies (e.g., targeting tumor necrosis factor-α), and genetic defects of the interferon-gamma receptors and signaling pathways [26]. Structural lung disease from chronic obstructive pulmonary disease (COPD), cystic fibrosis, and bronchiectasis have also conferred increased risk of NTM disease [27,28]. For similar reasons, SOT recipients may be at increased risk of NTM disease due to immunologic and structural abnormalities.

First, the immunosuppressive drug regimens (or the net state of immune-suppression) may promote the progression to clinical disease among those with environmental exposures (or those colonized with NTM), with a higher risk among those with augmented immunosuppression, such as those treated for acute or chronic cellular rejection [29]. To our *knowledge, however, no studies have specifically looked at rate of progression and no particular immunosuppressive drug is associated with a higher risk for NTM.*

Second, the disruption of mucocutaneous barriers (during surgery or the need for vascular access catheters) may serve as portals of entry for NTM. Third, structural abnormalities may promote airway colonization and disease, particularly among lung transplant recipients with impaired mucociliary clearance. Patients with cystic fibrosis, for example, are often *colonized or infected with NTM prior to transplantation. For most patients, this does not preclude transplantation, but patients have to undergo prolonged treatment even after organ transplantation [30].* It is very likely that other additional host-immune or structural local factors are involved in the development of NTM disease, but these have yet to be identified [24].

A case-control single-center study by Longworth et al. [3] sought to identify clinical and demographic risk factors associated with NTM disease in the transplant population. During a period of 7 years, they identified 34 SOT recipients with NTM disease, and the majority (71%)were male, with a median age of 54 years. Slightly over half of the cases (54%) occurred among lung transplant recipients. NTM disease developed relatively early, after a median of 8 months (IQR: 2–87 months), after transplantation. There was wide diversity in the causative species, but *M. abscessus* was the most common, followed by *M. avium complex*. The sites of infection also varied from pleuropulmonary disease, to cutaneous and deep tissue, intra-abdominal, and disseminated infections. Univariate analysis identified lung transplant recipients are at highest risk (OR 11.49, $p < 0.01$) and having developed biopsy-proven acute rejection also significantly increased the risk (OR 4, $p < 0.03$) of NTM disease. The results of this study validates the theory that structural abnormalities, exposure of the transplanted lung to potential environmental pathogens, and the advanced state of immune suppression in lung transplant recipients all contribute to the higher risk of NTM infection.

4. Clinical presentation

The clinical manifestations of NTM infections in SOT recipients are usually protean in nature. Accordingly, establishing the diagnosis may be difficult based on clinical symptoms alone. Hence, clinicians should have a high index of suspicion and a low threshold to obtain diagnostic specimens for mycobacterial culture. The most common clinical presentation of NTM disease among SOT recipients is cutaneous or osteoarticular in nature [2]. In general, NTM disease can be classified into one of six categories – pleuropulmonary, skin and soft tissue (including those with secondary dissemination), musculoskeletal (osteoarticular), bloodstream (including catheter-associated), lymphadenitis, and disseminated or multi-organ disease. Data on the isolates and clinical presentations from these cases are included in Table 1.

4.1. Lung transplant

Lung transplant recipients are unique among SOT recipients because they are often colonized with NTM prior to transplantation due to structural damage from underlying pulmonary disease. In fact, lung recipients who have a history of colonization with *M. abscessus* often develop progression to clinical disease after transplantation, despite adequate anti-mycobacterial therapy. As such, colonization with multi-drug resistant NTM prior to transplantation is considered a relative contraindication to lung transplantation by some centers [30–32].

Not surprisingly, the most common site of NTM disease after transplantation is pleuropulmonary [3,23,24,30,32–36], with *M. abscessus* as the most commonly isolated species, followed by MAC. These patients with pulmonary NTM disease often present with chronic productive cough, shortness of breath, pleuritic pain, and/or fever and chills [23,34]. CT scan findings are variable but classically show nodular or tree-in-bud findings [23].

Although pulmonary disease is by far the most common presentation, NTM infections in lung transplant recipients may present as disseminated [3,24,31,32,34,36–41], osteoarticular [24,30,37], and cutaneous [3,34,42] disease.

4.2. Non-lung transplant

4.2.1. Kidney

Among the SOT population, kidney transplant recipients have the most reported number of NTM infections with a total of 148 cases to date [3,9,10,12–20,36,43–121]. This is likely due to the relatively large numbers of kidney transplants performed, compared to other SOT. The most common manifestation among these patients is local cutaneous disease including cases with secondary

Table 1
Clinical presentation of NTM disease in solid organ transplant recipients.

Type of transplant	Reference	Patients (*n*)	Gender M/F	Age, median (yr)	Median time to onset (mos)	Mycobacterium species	Type of infection
Lung							
Lung	[3,23–25,30–35,37–42, 150–155]	102	48/35	42.2	13.3	MAC, 26; M. abscessus, 59; M. hemophilum, 4; M. fortuitum, 2 M. marinum, 2; M. kansasii, 2; M. asiaticum, 1; M. chelonae, 3 MAC+Abscessus, 1; M. simiae, 1 M. genavense, 1	Pleuropulmonary, 65 Cutaneous, 11 Osteoarticular, 9 Disseminated, 17 Other, 0
Non-lung							
Kidney	[3,9,10,12–20,36,43–121]	148	87/53	45	27	MAC, 15; M. gordonae, 4; NTM NOS, 14; M. xenopi, 7 M. chelonae, 31; M. abscessus, 9 M. fortuitum, 12; M. haemophilum, 13 M. kansasii, 24; M. genavense,7 M. scrofulaciecum, 2; M. immunogenum, 1;M. marinum, 6 M. gastri,1; M. terrae, 1; Mult, 1	Pleuropulmonary, 23 Cutaneous, 51 Cutaneous, with dissemination, 5; Osteoarticular, 31; Disseminated, 22; Other, 16
Heart	[21,53,96,107,135–149]	33	25/5	47	33	*M. kansasii, 9; MAC, 8; M. hemophilum,5; M. scrofulaceum, 1; M. chelonae, 2; M. theroresistibile,2 NTM NOS, 2; M. fortuitum, 1; M. genavense, 3*	Pleuropulmonary, 6 Cutaneous, 9 Cutaneous with dissemination, 4 Osteoarticular, 3 Disseminated, 11
Liver	[3,53,76,96,122–134]	21	5/12	51	24	MAC, 7; M. xenopi, 1; M. chelonae, 1 M. abscessus, 3; M. hemophilum, 2 M. genavense, 2; M. marinum, 1 M. llatzerense,1; M. mucogenicum, 1 M. triplex,1; Mult, 1	Pleuropulmonary, 7 Cutaneous, 4 Cutaneous with dissem, 2 Osteoarticular, 2 Disseminated, 4 Other, 2

cutaneous dissemination, followed by osteoarticular disease. *Cutaneous NTM disease often manifests as painless, violaceous nodules that may ulcerate and commonly follow a sporotrichoid appearance.* The most common NTM species is *M. chelonae,* followed by *M. kansasii.*

4.2.2. Liver

To date, there are only 21 cases of NTM reported among liver transplant recipients [3,53,76,96,122–134], despite the increasing volume of liver transplantations. The underlying reason for the rarity of NTM cases among liver transplant cases is not known. Among all cases reported, the most common clinical presentations were pleuro-pulmonary followed by cutaneous disease. *In general, those with pleuro-pulmonary disease presented with cough, fever or chills, shortness of breath, or a combination thereof. MAC was the most common species isolated, accounting for one-third of all isolates.*

4.2.3. Heart

Like liver transplant recipients, NTM disease among heart transplant recipients appears to be rare. There have only been a total of 33 cases reported in the literature [21,53,96,107,135–149]. *M. kansasii* was the most frequently isolated NTM species, and 39% (13/33) cases presented with cutaneous disease, half of which had secondary dissemination.

5. Diagnosis

5.1. Clinical diagnosis

The diagnosis of NTM disease in transplant recipients is often difficult. Establishing a diagnosis of pulmonary infection, especially among lung transplant recipients, can be challenging because NTM isolates recovered from sputum samples may represent colonization. Given the diagnostic dilemma, the American Thoracic Society (ATS) published guidelines on the diagnosis and treatment of disease due to NTM [27]. A combination of clinical, radiographic, and bacteriologic criteria is required for diagnosis of NTM pulmonary disease (Table 2). Similarly, extrapulmonary disease is diagnosed through a combination of clinical and microbiologic findings with or without adjunctive histologic confirmation.

Since NTM infections are rare, they are not often included in routine diagnostic testing. Hence, a high level of clinical suspicion for NTM disease is essential for rapid and accurate diagnosis. Frequently, time to clinical presentation from transplantation can be long, with a median of 13.3 months among lung transplant patients [23–25,31–35,37–42,150–155], and even longer (range of 24–33 months) among other SOT recipients. Since the infection may occur at any time, NTM disease has to be considered with any unexplained febrile illness, surgical site or bone infection, non-healing wound or cutaneous lesion, or pleuropulmonary disease, especially when routine bacterial cultures are non-diagnostic. Often, the first indication of an NTM disease is the absence of bacterial growth on routine cultures. In these instances, and whenever there are suspicious lesions in a transplant recipient, clinical samples and tissues should be obtained for histologic and microbiologic examination. Often, repeated sampling may be necessary to establish the diagnosis. It is important to emphasize that although granulomas on histopathology are suggestive of possible NTM disease, the absence of granulomatous lesions does not necessarily negate the diagnosis in transplant recipients who have attenuated immune responses.

5.2. Laboratory diagnosis

To confirm the clinical suspicion of NTM disease, clinical samples should be sent to the microbiology laboratory for acid fast staining, mycobacterial cultures, and histopathology. The laboratory should be informed that NTM is a clinical consideration in order to guarantee proper media selection, temperature incubation, and duration of culture growth. Some NTM species are fastidious organisms and have specific growth requirements. *For example, M. haemophilum and M. marinum both grow best between* 28–30 °C. *However, M. haemophilum requires media supplemented*

Table 2
Clinical and microbiologic criteria for diagnosing nontuberculous mycobacterial lung disease [27][a].

Clinical (both required)
1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules (A, I)[a]
AND
2. Appropriate exclusion of other diagnoses (A, I)
Microbiologic
1. Positive culture results from at least two separate expectorated sputum samples (A, II). If the results from (1) are nondiagnostic, consider repeat sputum AFB smears and cultures (C, III).
OR
2. Positive culture result from at least one bronchial wash or lavage (C, III)
OR
3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM (A, II)
OTHER
4. Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination (C, III)
5. Patients who are suspected of having NTM lung disease but do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded (C, III)
6. Making the diagnosis of NTM lung disease does not, per se, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients (C, III)

with iron-containing compounds such as ferric ammonium citrate, hemin, or hemoglobin, while M. genavense requires mycobactin [27].

*The Interferon Gamma Rapid Assays (IGRAs) are not useful in the diagnosis of NTM. However, is important to know that the target antigens used (*e.g. *ESAT-6 and CFP-10) which are present in M. tuberculosis, are also present in some other mycobacteria, including M. kansasii and M. marinum. As such, there is some cross-reactivity. The diagnostic usefulness of the IGRAs has not been validated for NTM, however, and they are not recommended for diagnoses [156],[157].*

Identification of the NTM to the species or subspecies level is necessary for epidemiologic, prognostic and therapeutic considerations. In referral laboratories, speciation may be accomplished by molecular probes and 16S rDNA sequencing [27]. Knowledge of the NTM species is necessary for choosing an empiric regimen. In addition, determination of the antimycobacterial susceptibilities of certain NTM species is recommended to guide the final targeted antimycobacterial therapy.

6. Treatment

A detailed review of the treatment regimens used for specific NTM disease is beyond the scope of this review article, and the ATS guideline is available for reference [27]. Nevertheless, some key features of treatment of NTM disease among SOT recipients merit emphasis. *First, asymptomatic colonization is often not treated prior to transplantation or re-transplantation. However, in patients who are symptomatic, with a high burden of organism, such as in CF patients colonized with NTM, one basic tenet is to try and reduce mycobacterial burden prior to transplantation, and to continue to treat aggressively during the immediate period after transplantation [158]. Duration of treatment is influenced by the offending pathogen and drug tolerability.* Second, whenever possible, reduction of immunosuppression should be considered among SOT recipients to aid in the clearance of infection and/or minimize drug interactions. Third, other contributing factors, such as concomitant viral infections (in particular, CMV infection) should be treated. [2] Fourth, the choices of antimicrobial drugs for treatment are similar to those recommended for non-immunosuppressed patients. However, interactions between medications for NTM and the immunosuppressive agents are anticipated. The rifamycins, which are the backbone for treating some NTMs such as MAC, are potent cytochrome P450 (CYP450) inducers and will expectedly reduce the blood levels of calcineurin and mammalian target of rapamycin (mTOR) inhibitors. If the dose of these drugs are not adjusted accordingly when rifamycins are initiated, it may lead to subtherapeutic levels and could lead to allograft rejection. Compared to Rifampin, Rifabutin is a less potent inducer of CYP450, and is the preferred agent for treatment among transplant recipients. In contrast, the macrolide antibiotic such as Clarithromycin is a potent CYP450 inhibitor, and could have the reverse effect. Azithromycin has minimal in vitro inhibitory effect on CYP450 and is the preferred macrolide for the transplant population. Often, a combination of a macrolide and rifamycin is needed for treatment, and thus, the level of calcineurin inhibitors should be monitored closely and drug doses adjusted accordingly.

In general, combination antimycobacterial therapy for a prolonged period of time is the rule for treatment of NTM disease. More than one active agent is necessary for treatment to avoid interval development of resistance during therapy. In patients with severe or disseminated disease and high organism burden, a minimum of 3 active drugs should be considered for induction treatment, followed by de-escalation to dual treatment during maintenance therapy. *Often, treatment is continued until there is documentation of multiple negative cultures.*

The choice of antimycobacterial agents and duration of therapy are largely dependent on the specific NTM isolate, given the wide variability of in vitro susceptibility patterns. Although recommendations exist for treatment duration for specific diseases due to NTM, this is often considered minimum duration of treatment among transplant recipients, as response to treatment in this population of patients is often delayed, and microbiologic cures are difficult to achieve. This prolonged exposure to a variety of drugs also leads to significant toxicity, which is heightened in this population of patients.

There are also other interventions that should complement standard anti-NTM medical therapy. In addition to reducing immunosuppression, one should advocate for timely surgical resection, debridement of fluid collections or devitalized tissue, or removal of infected devices in order to decrease organism bioburden and reduce the risk of drug resistance. *In cases where devices cannot be safely removed, prolonged suppressive therapy, usually with multiple oral agents, if feasible, is recommended.*

The use of secondary prophylaxis for NTM infections in the transplant population remains controversial. If selected, it should be based on available susceptibility data and discussed in detail with experts in treating such infections in complex patients.

A summary of treatment recommendations based on existing guidelines for selected NTM species is provided in Table 3.

Table 3
Treatment regimens for selected NTM species in transplant recipients.

Organism	Recommended regimen	Alternative/second line drugs	Duration	Other
SGM				
M. avium complex	AZM 250–500 mg/d +RFB 300 mg/d + EMB 15 m/k/d±AMK IV	RIF, CLR, AMK, MXF	12 mos of negative sputum cultures (for pulmonary dse)	
M. kansasii	RFB 300 mg, EMB15m/k/d, INH 5/m/k/d + Pyridoxine 50 mg/d If with RIF resistance-3 drug regimen based on in-vitro susceptibilities	AZM, MXF, SXT, STR	12 mos of negative sputum cultures (for pulmonary dse)	
M. marinum	Two active agents, usually AZM + EMB	RIF/RFB,CLR, EMB, DOX	3–4 mos	Uniformly resistant to INH/PZA
RGM				
M. abscessus	Must be based on in-vitro susceptibility data: AZM 250 mg/d plus IV (AMK, FOX, IPM)	LZD, TGC Linezolid, tigecycline	4–6 mos	Uniformly resistant to anti-TB drugs
M. chelonae	Must be based on in-vitro susceptibility data: AZM plus (1) other agent (TOB, LZD, IPM)	AMK, DOX, CIP	4–6 mos	
M. fortuitum	At least 2 active agents with in vitro activity	AMK, CIP, SXT, FOX, IPM, AZM, DOX	12 mos of negative sputum cultures (for pulmonary dse) 4-6 mos for SSTI or bone-joint	Inducible resistance to MAC
Fastidious NTM				
M. haemophilum	No standardized susceptibility data	AMK, AZM, CIP, RIF, RFB,	Not determined	Uniformly resistant to EMB
M. genavense	AZM + at least one other active agent	AMK, RFB/RIF, CIP, AZM, STR	Not determined	EMB with limited activity
M. gordonae	Must be based on in-vitro susceptibility data	EMB, RFB, AZM, LZD, CIP	Not determined	Most frequently isolated contaminant

AZM – Azithromycin, RFB – Rifabutin, AMK – Amikacin, CLR- Clarithromycin, MXF – Moxifloxacin, SXT – Trimethoprim-sulfmethoxazole, STR – Streptomycin, FOX – Cefoxitin, IPM – imipenem, LZD – Linezolid, TGC – tigecycline, DOX – Doxycycline, CIP – ciprofloxacin, MAC – macrolides, PZA – Pyrazinamide.

7. Outcome

The prognosis of NTM disease in transplant recipients is highly variable, due to multiple factors including type of transplant, immune suppression, site and extent of NTM infections, and the specific NTM species. Overall, there is a high rate of treatment failure, as detailed below. Prognosis is worse, and may lead to death, particularly among SOT patients with disseminated disease.

7.1. Lung transplant recipients

Among the 102 cases of NTM infection in lung transplant recipients, information regarding outcomes are available among 79 patients [25,30–32,35,37–40,42,150,152–155]. Of these, 33 were reported to have been cured, cleared of infection, or culture negative at the end of treatment; 11 had some improvement, 3 had recurrence, while 7 had either no response or minimal response. Death occurred in 25 patients, with mortality attributed to NTM among 8 patients with either pleuropulmonary or disseminated disease; notably, 7 of 8 deaths were from *M. abscessus*; the remaining one from *M. genavense*.

There were 2 recent series that looked specifically at *M. abscessus* [30,32]: among the 5 patients reported by Qvist, 1 patient cleared the infection, 2 patients were clinically well despite persistently positive cultures, while 2 died but due to non-NTM related causes. Outcomes of patients in the study by Lobo were slightly better, with 3 patients clearing the infection, and 1 with death related to disseminated *M. abscessus*.

7.2. Non-lung transplant recipients

7.2.1. Kidney

Among all cases of renal transplant recipients with NTM disease, data regarding outcome was available for 124/148 cases [9,10,12,16–18,20,43–52,54–80,82–114,116–121]. Sixty two percent (77/124) reported cure with initial therapy, and 14 (11%) had considerable improvement during ongoing treatment. However, 10 (8%) had disease recurrence, and 3 (2%) had persistent or progressive disease requiring either change in medical management and/or surgical intervention. Disease recurrence or persistence was associated with either osteoarticular or cutaneous disease, although there was no predominant NTM species. There were 8 deaths (6%) attributed to NTM-disease [12,17,45,73,76,95]. All deaths with the exception of one [80] was from disseminated disease; the underlying NTM species causing disseminated NTM infection was varied, and included *M. kansasii, M. fortuitum,* MAC, and *M. genavense.*

7.2.2. Liver

Of the 21 cases of NTM in liver transplant recipients, outcome was reported for 17 of them [53,76,96,122–134]. Outcome was favorable in most liver recipients, with the majority of patients (11/17) being cured, or having disease improvement by the time of follow up (1/17). Death occurred in 4 cases, but only one was attributed to disseminated NTM disease, from *M. genavense* infection [53].

7.2.3. Heart

Among heart transplant recipients, outcome was reported on 17 cases [21,53,96,107,136–145,147–149]. Of these, 8 were cured, 1 improved on treatment, and 3 had either recurrence or progression of disease. Of the five deaths, three were attributed to disseminated disease from NTM [21,107,145], of varying species (*M. genavense*, MAC, and NTM not specified).

8. Conclusion

NTM disease among transplant patients remains infrequent, although its incidence appears to be increasing. This most likely reflects improvement in microbiological techniques and improved survival from transplantation. Although NTM infection is a

relatively uncommon, the risk of NTM disease is many-fold greater in transplant recipients than in the general population.

Among all transplant recipients, lung transplant recipients are more prone to develop NTM disease, although it is more commonly reported among kidney recipients, likely due to the higher volume of kidney transplants.

The clinical presentation of NTM disease in the transplant population is protean in nature, and can be very difficult to diagnose, both clinically and microbiologically. It differs substantially from NTM disease associated with HIV-AIDS, which is more often than not disseminated MAC. In the transplant population, the clinical presentation varies depending on the underlying transplant, and can be insidious in nature. The treatment regimen for NTM disease in transplant patients is the same as in the non-transplant population, although it is often more complicated given potential drug–drug interactions between antimycobacterial and immunosuppressive agents.

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