

## Mycobacterial infections in heart transplant recipients

### *Kalp nakli alıcılarında mikobakteriyel enfeksiyonlar*

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#### ABSTRACT

Mycobacterial infections frequently develop as a consequence of immunosuppression and are often a causative cause of morbidity and mortality. Epidemiology and clinical characteristics of mycobacterial infections after solid organ and stem cell transplantation have been well-described. However, due to the rarity of clinical data, the pertinent aspects of mycobacterial infection after heart transplantation remain to be clarified. A comprehensive literature collection revealed mycobacterial infections after heart transplantation usually developed late after transplantation. Cutaneous and pulmonary infections were the most common with *Mycobacteria tuberculosis* being the prevailing pathogen. Unlike in solid organ transplant recipients, non-tuberculous mycobacterial infections in heart transplant recipients were sporadic with no prevailing species. Combined drug therapy seemed to be more effective than monotherapy. The overall survival rate was 84.2%.

**Keywords:** Heart transplantation; microbiology; mycobacterium.

Mycobacterial infections frequently develop as a consequence of immunosuppression and are often a causative cause of morbidity and mortality.<sup>[1]</sup> *Mycobacterium (M.) tuberculosis* in solid organ transplant recipients has a much higher mortality rate than overall population.<sup>[2]</sup> *M. tuberculosis* has been reported to represent 6.7% of lung infections in solid organ transplant recipients,<sup>[3]</sup> while *M. abscessus* and *M. avium* complex are the most common pathogens of non-tuberculous mycobacteria (NTM) infections and the lung was the most common infection site.<sup>[4]</sup> Non-tuberculous mycobacteria infections developed

#### ÖZ

Mikobakteriyel enfeksiyonlar sıklıkla immünsüpresyon sonucunda meydana gelir ve genellikle morbidite ve mortalitenin nedenidir. Katı organ ve kök hücre naklinden sonra mikobakteriyel enfeksiyonların epidemiyoloji ve klinik özellikleri iyi tanımlanmıştır. Ancak, klinik verilerin ender olması nedeniyle, kalp nakli sonrasında mikobakteriyel enfeksiyonlara ait özellikler henüz aydınlatılmamıştır. Kapsamlı bir literatür taraması, kalp nakli sonrasında mikobakteriyel enfeksiyonların genellikle nakilden sonra geç dönemde ortaya çıktığını gösterdi. Kütanöz ve pulmoner enfeksiyonlar, en sık baskın patojen olarak *Mycobacteria tuberculosis* ile birlikte idi. Katı organ nakil alıcılarının aksine, kalp nakli alıcılarında tüberküloz dışı mikobakteriyel enfeksiyonlar, belirli bir baskın suş olmaksızın, sporadikti. Kombine tedavinin monoterapiden daha etkili olduğu görüldü. Genel sağkalım oranı, %84.2 idi.

**Anahtar sözcükler:** Kalp nakli; mikrobiyoloji; mikobakteri.

eight months (interquartile range: 2 to 87 months) after solid organ transplant with lung transplant recipients at the highest risk of the infection.<sup>[4]</sup> In heart transplant recipients, the etiopathogenesis of mycobacterial infections include exacerbation of a silent infection after transplantation as a result of immunosuppression, new infection of the immunosuppressed recipient after transplantation, and direct transmission of infection from the donor. According to the duration of latency, mycobacterial infection can be categorized into early ( $\leq 3$  months), intermediate (3 to 12 months), and late ( $\geq 12$  months) presentations.<sup>[5]</sup> The early presentation can



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be a consequence of intraoperative infection, whereas late infections may result from post-transplantation immunosuppressive therapy.<sup>[5]</sup> Epidemiology and clinical characteristics of mycobacterial infections after solid organ or stem cell transplantation have been well-described in the literature.<sup>[6,7]</sup> However, due to the rarity of clinical data, the pertinent aspects of mycobacterial infections after heart transplantation still remain to be clarified. This study aims to present the clinical characteristics, management and prognosis of the patients with mycobacterial infections after heart transplantation.

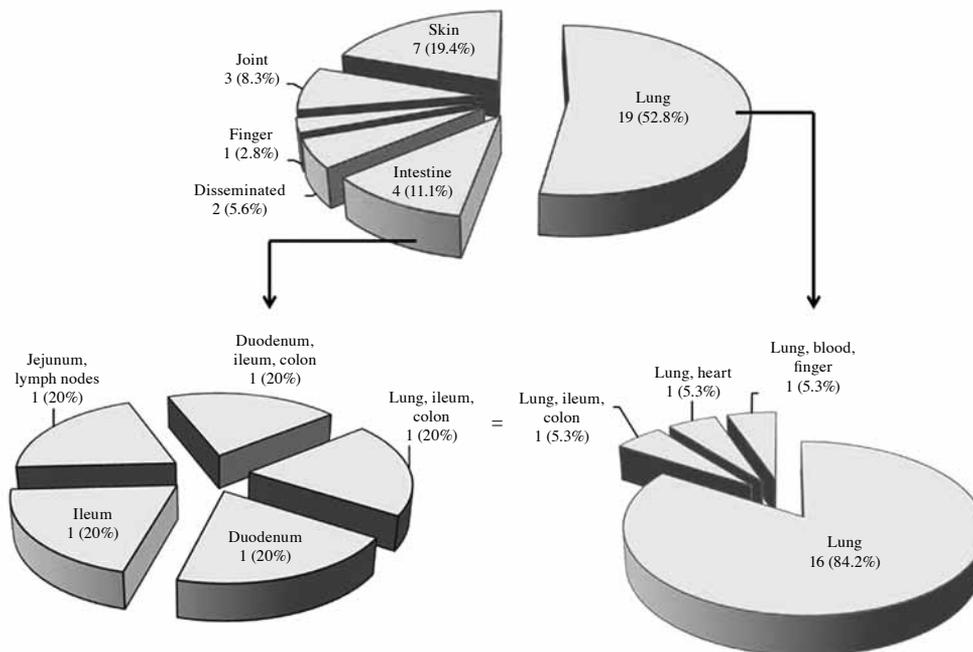
**MATERIALS AND METHODS**

MEDLINE, Highwire Press and Google search engine were searched for publications in the English language between January 2000 and March 2013 on mycobacterial infections after heart transplantation. The major search terms were “Mycobacterium” and “heart transplantation”. “*Mycobacterium tuberculosis*”, “non-tuberculous mycobacteria”, “atypical mycobacterium”, and “*M. spp.*” were also searched for the completeness of the retrieval. All the articles, titles, and subject headings were screened carefully to find a potential relevance. Mycobacterial infections after heart-lung transplantation were excluded. Data for collection included patients’ demographics, time from heart transplantation to mycobacterial infection, samples for analysis, analysis methods, infection site, mycobacteria, drug therapy, and prognosis.

**RESULTS**

There were totally 23 articles<sup>[5,8-29]</sup> including 17 (72.7%) case reports,<sup>[8-24]</sup> five (22.7%) original articles<sup>[5,25-28]</sup> and one (4.5%) Letter to the Editor<sup>[29]</sup> with 39 patients involved. Of these patients, there were 33 males and 4 females with a male-to-female ratio of 8.3:1, while two patients’ sex was unknown. The mean age was 56.4±8.9 (range, 37 to 69; median, 58) years (n=39).

The mean time from heart transplantation to mycobacterial infection was 36.5±28.2 (range, 0 to 96; median, 36) months (n=27). The mean latency was 36.0±23.1 (range, 3 to 67; median, 37) months (n=11) for lung infections<sup>[5,9,10,21,24-28]</sup> and 36.9±31.9 (range, 0 to 96; median, 47) months (n=16) for non-lung infections<sup>[8,11-20,22-26,29]</sup> (p=0.9400). A delayed diagnosis of mycobacterial infection was made in nine (23.7%) patients over a mean time of 48.8±49 (range, 3 to 144; median, 36) months from transplantation to diagnosis (n=9). The major infection sites were lung and skin (Figure 1). Sole lung infections were more common than combined infections of lung and other organs and totally five intestinal infections were reported (Figure 1). Mycobacterium was analyzed in 36 patients: 23 (63.9%) patients had one sample,<sup>[5,11,12,14,16-18,24-28]</sup> six patients (16.7%) had two samples,<sup>[9,10,15,19,21,23]</sup> five patients (13.9%) had three samples,<sup>[8,10,13,22,26]</sup> one patient (2.8%) had five samples<sup>[20]</sup> and one patient (2.8%) had eight samples.<sup>[29]</sup> Of 63 samples, biopsy and sputum were the two most common specimens and the biopsy



**Figure 1.** Sites of mycobacterial infections.

samples were prevailed by skin and lymph nodes, for investigation of mycobacteria (Figure 2). The biopsied lymph nodes were taken from the mediastinum in three (37.5%), mesenterium in two (25.0%), neck in two (25.0%) and epitrochlea in one patient (12.5%); while the lesions biopsied were those of the duodenum, neck, arm, and jejunum in one (25%) patient each.

Microbiology of all analyzed samples showed high sensitivity and histopathology of only biopsy and sputum samples showed high sensitivity for mycobacterial inspections. Polymerase chain reaction (PCR) was also used to determine the species of the mycobacteria (Table 1).

Of the 39 mycobacteria, *M. tuberculosis* was the most common representing 55.3%.<sup>[10,18,24-28]</sup> Besides, there were three cases (7.9%) of *M. leprae*,<sup>[15,17,19]</sup> and two (5.3%) avium complex infections.<sup>[11,20]</sup> *M. spp.* (other than *M. tuberculosis*, *M. bovis*, *M. avium*, or *M. leprae*) of the remaining 12 patients included *M. abscessus*,<sup>[5,14,22]</sup> *M. genavense*,<sup>[12,29]</sup> *M. haemophilum*,<sup>[13,23]</sup> *M. xenopi*,<sup>[9,10]</sup> *M. kansasii*,<sup>[8]</sup> and *M. chelonae*,<sup>[16]</sup> and the species of one atypical mycobacteria was not determined<sup>[21]</sup> (Figure 3). One patient with *M. xenopi* infection had a co-infection of *Pseudomonas aeruginosa*.<sup>[10]</sup>

Anti-mycobacterial regimens were described in 34 patients: a 2-combined in one (2.9%),<sup>[5]</sup> a

3-combined in 13 (38.2%),<sup>[10,11,13-20,22-26]</sup> a 4-combined in 17 (50%),<sup>[8-10,12,24-26]</sup> a 5-combined in one (2.9%)<sup>[29]</sup> and a 6-combined antibiotic regimen in two patients (5.9%),<sup>[26]</sup> respectively.

The distributions of the anti-mycobacterial agents used in 34 patients showed that the anti-tuberculous agents were the most commonly used (Figure 4). The duration of the anti-mycobacterial agent use was 11.2±4.8 (range, 4 to 21; median, 12) months (n=26). During the treatment, six patients (13.2%) showed anti-mycobacterial renal toxicity (n=3),<sup>[11,14,15,23]</sup> cyclosporine intoxication (n=1),<sup>[10]</sup> or gastrointestinal adverse reactions (n=3),<sup>[10,13,15]</sup> to seven drugs used in eight patients including cyclosporine (n=2), rifampin (n=1), moxifloxacin (n=1), doxycycline (n=1), clarithromycin (n=1), amikacin (n=1) and aminoglycoside (n=1), leading to discontinuation, reduction, or change of drug. A significant interaction between cyclosporine concentrations and antibiotic treatment was noted in eight (20.5%) patient, in whom a 3~6-fold of cyclosporine dose was required for maintaining the therapeutic levels during antibiotic therapy.<sup>[10,26]</sup>

Multiple logistic analyses revealed that patient's sex, age, immunosuppressive agent with cyclosporine, onset time of mycobacterial infection, lung infection, *M. spp.* infection and graft rejection were not found to be predictive risk factors for mortality (Chi-square =29, p=0.739).

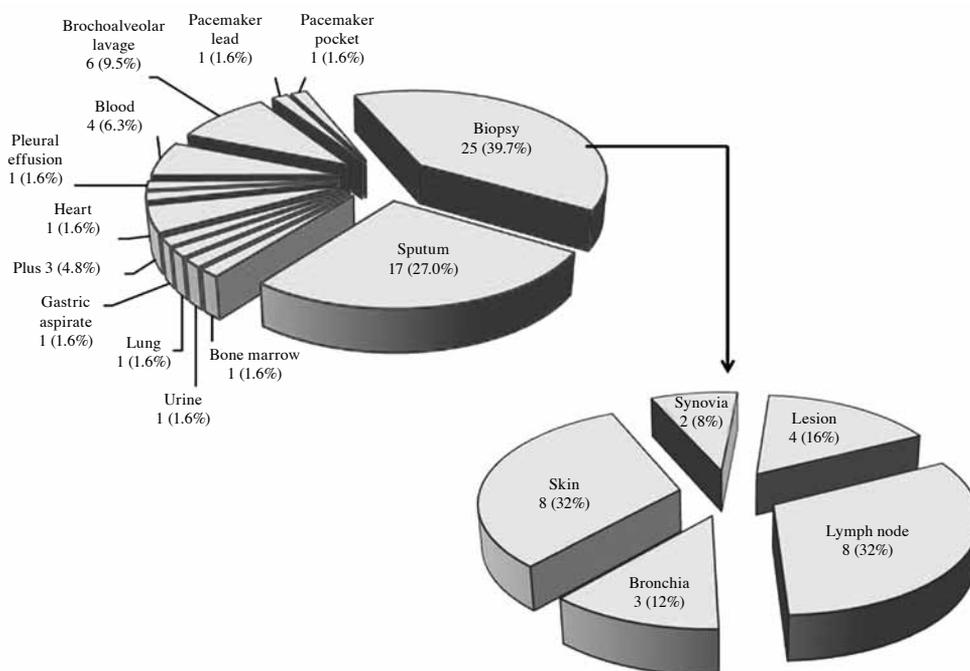


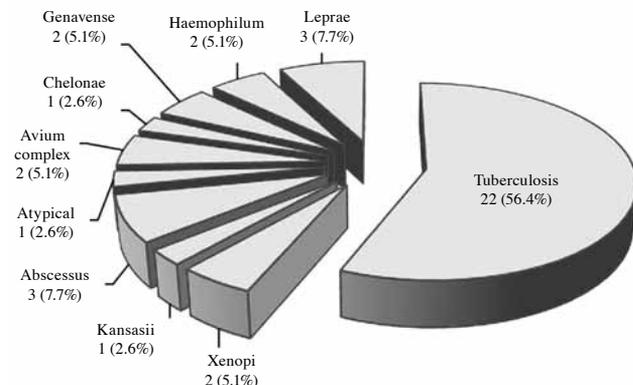
Figure 2. Samples for mycobacterial analysis.

**Table 1. Results of mycobacterial analysis of samples**

Sample	Analysis								
	Microbiology			Histopathology			Molecular biology		
	n	%	p	n	%	p	n	%	p
<b>Biopsy</b>									
Positive	13	61.9	} 0.1228	22	88	} 0.0000	6	60	} 0.3711
Negative	8	38.1		3	22		4	40	
<i>Chi square</i>	2.4			28.9			0.8		
<b>Sputum</b>									
Positive	14	100	} 0.0000	0	0	} 0.0143	0	0	} -
Negative	0	0		2	100		0	0	
<i>Chi square</i>	42.0			6.0			--		
<b>Bronchoalveolar lavage</b>									
Positive	3	100	} 0.0027	1	50	} 1	0	0	} -
Negative	0	0		1	50		0	0	
<i>Chi square</i>	9.0			0			--		
<b>Others</b>									
Positive	10	100	} 0.0000	3	60	} 0.5271	4	80	} 0.0578
Negative	0	0		2	40		1	20	
<i>Chi square</i>	20.0			0.4			3.6		
<b>Total</b>									
Positive	40	83.3	} 0.0000	26	76.5	} 0.0000	10	66.7	} 0.0679
Negative	8	16.7		8	23.5		5	33.3	
<i>Chi square</i>	42.7			19.1			3.3		

Interventions were necessary in two patients including pacemaker and atrial lead removal in one patient<sup>[22]</sup> and ankle aspiration in another.<sup>[8]</sup>

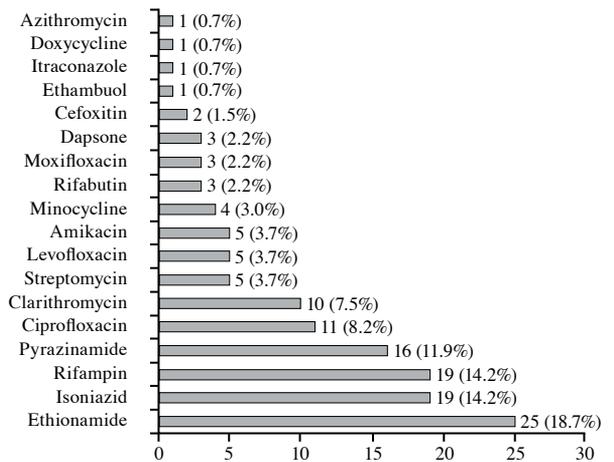
The mean follow-up was 27.5±35.6 (range, 1 to 120; median, 15) months (n=12). Prognoses of the patients were described in 38 patients: 26 (68.4%) had a complete recovery (one of them was complicated with spinal diskitis and osteomyelitis), five (13.2%) had a significant improvement, one (2.6%) had no progress and six (15.8%) died. The overall survival was 84.2%.



**Figure 3.** Mycobacterial pathogens.

**DISCUSSION**

Although symptoms of post-transplantation mycobacterial infections range from localized lesions of the skin and soft tissue, lungs and lymph nodes to disseminated infections, the most common initial symptoms are cutaneous and pulmonary.<sup>[30]</sup> In the recipients of solid organ transplant including heart transplant with *M. abscessus* infection, localizations of infections predominated by skin



**Figure 4.** Anti-mycobacterial agents.

and lung infections.<sup>[5,30]</sup> The median interval from transplantation to diagnosis was 24 months (range, 7 days to 276 months).<sup>[5]</sup>

Ziehl-Neelsen method showed low sensitivity.<sup>[31]</sup> However, acid-fast bacilli were observed in 75% of the analyzed samples.<sup>[5]</sup> Respiratory and cutaneous samples were predominant with skin lesions being the major source of the primary symptoms prior to disseminated infection.<sup>[5]</sup> The present study further conforms these results. Ray et al.<sup>[21]</sup> reported that the causative mycobacterial species were unable to be identified due to the absence of species-specific PCR. Guitard et al.<sup>[29]</sup> demonstrated that the duodenal and lymph node biopsied specimens were negative by PCR for 16S rRNA. However, Ziehl-Neelsen staining showed numerous acid-fast bacilli. The results of PCRs were negative for *M. tuberculosis* and *M. avium*, but positive for *M. spp.* One patient had high performance liquid chromatography detected for isolation of mycobacterial series.<sup>[13]</sup>

In the transplant recipients, *M. tuberculosis* infection may cause graft dysfunction, being responsible for the increased mortality.<sup>[2,32,33]</sup> Interactions between anti-tuberculous agents (rifampicin, in particular) and the calcineurin inhibitors (cyclosporine and tacrolimus) may enhance the graft rejection.<sup>[2,33,34]</sup> Comerci et al.<sup>[11]</sup> investigated the possibility of hematopoietic donor-receipt chimera as a possible etiology of mycobacterial infection; however, the authors reported negative results. Due to the fact that the limit of detection was only 3%, chimera was unable to be completely excluded in <3% of the donors and >97% of the recipients. The prevailing NTM in solid organ transplant recipients were *M. avium* complex (32%) and *M. kansasii* (28%).<sup>[2]</sup> Non-tuberculous mycobacteria infections usually develop in the late stage of solid organ transplantation (range, 86 days to 11.5 years; median, 15 months).<sup>[2]</sup> In this study, I found that the time interval from heart transplantation to mycobacterial infection were even longer. Proposed risk factors for infection due to NTM in heart transplant recipients were previous heart operation, history of opportunistic infections, and enhanced immunosuppressive management due to the recent acute rejection.<sup>[2]</sup>

The presence of intestinal disease is rare in heart and solid organ transplant recipients.<sup>[2]</sup> As monotherapy may cause drug resistance easily,<sup>[35]</sup> combined drug regimen are recommended, as it was suggested in the present study. Clarithromycin and azithromycin are the most active drugs against *M. avium* complex. The initial treatment regimen for NTM infection should include a macrolide plus ethambutol and a third drug

with either clofazimine, rifabutin, or ciprofloxacin.<sup>[36]</sup> Reducing immunosuppression therapy may play a role in the management of disease due to NTM infection.<sup>[2]</sup> The cure rate was 64% and NTM infection-related death was 8%.<sup>[2]</sup>

The management of tuberculosis in solid organ transplant recipients is challenging due to the side effects of anti-tuberculous drugs and their potential interactions with immunosuppressive agents.<sup>[5]</sup> Drug interactions may lead to graft rejection<sup>[5]</sup> and drug toxicity.<sup>[37]</sup> Interaction between itraconazole or clarithromycin and cyclosporine or pravastatin,<sup>[16]</sup> rifampin and cyclosporine,<sup>[17]</sup> and clofazimine and azathioprine<sup>[17]</sup> have been also studied. The reduced serum concentrations of immunosuppressive agents are presumed to be mediated by cytochrome P450 activation.<sup>[37]</sup> Therefore, drug therapy needs to be tailored to accommodate the immunosuppressant regimen.<sup>[17]</sup> Observations showed that cyclosporine A concentration increased between the second and fourth day after clarithromycin treatment was initiated.<sup>[38]</sup> Long-term rifampin therapy caused an over two fold reduction of dose-calibrated mycophenolic acid exposure, which may be interpreted by concurrent elicitation of visceral uridine diphosphate-glucuronosyltransferases and organic anion transporters which suppress mycophenolic acid.<sup>[39]</sup> Decline of use of rifampin and clofazimine and a modified leprosy regimen consisting of dapsone 100 mg, ethionamide 250 mg and minocycline 100 mg once daily have been proposed to avoid the potential drug interactions.<sup>[19]</sup>

Furthermore, the present study, for the first time, presents a comprehensive analysis of mycobacterial infections after heart transplantation. The latency from heart transplantation to mycobacterial infection was as long as over three years. Lung and skin were the most prevalent infection sites. Microbiological examination of all samples and histopathological examination of biopsy and sputum specimens showed high sensitivity for mycobacterial analysis. In addition, PCR was helpful in determining the species of the pathogen. *M. tuberculosis* was the most common with no prevailing *M. spp.* species. Combined drug therapy seemed to be more effective than monotherapy. The prognosis was similar to those of the solid organ transplant recipients (treatment success rate 85.7% and mortality 19%).<sup>[28]</sup>

In conclusion, mycobacterial infections were rare and usually developed late after heart transplantation. Cutaneous and pulmonary infections were the most common with *M. tuberculosis* being the predominant pathogen. Unlike in solid organ transplant recipients,

NTM infections were sporadic in heart transplant recipients with no prevailing species. I suggest that combined drug therapy is more effective than monotherapy in this patient population.

### Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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