Fungal Infections in Solid Organ Recipients

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Background: **Fungal infections are a major cause of morbidity and mortality after organ transplantation. The incidence of these infections has increased considerably over the last decade.**

Objectives: **The aim of this study was to evaluate the incidence of fungal infections, to identify the most common fungal pathogens, and to determine the associated risk factors in solid organ recipients.**

Methods: **One hundred twenty renal and 50 liver recipients were transplanted at the organ transplant unit of Nemazi Hospital in Shiraz, Iran, from September 2004 to August 2005 and were followed for fungal infections for at least 6 months. On admission to the hospital, all patients were evaluated for fungal colonization by mouth, vagina, urine, and rectal swabs cultured in Sabouraud Dextrose Agar. Samples of sputum, bronchoalveolar lavage, urine, cerebrospinal fluid (CSF), pleural tap, and tissue biopsy were evaluated by direct microscopic examination and were cultured for any clinical signs of fungal infections.**

Results: **Fifty-four kidney recipients (45%) had *Candida* colonization in different sites of their bodies. Fungal infections presented in 13 of 120 recipients (10.8%). Five recipients had invasive fungal infections (3 had fungal pneumonitis and 2 had severe esophagitis), and 8 patients had cutaneous and mucocutaneous infections. All of the recipients with invasive fungal infections were colonized with *Candida*, and 2 of them died.**

Forty-two (84%) liver recipients had *Candida* colonization in different sites of their bodies. Fungal infections presented in 6 liver recipients. In 4 patients, invasive fungal infections occurred (2 fungal pneumonitis, 1 meningitis, and 1 severe esophagitis), 2 patients showed mucocutaneous infections. Three recipients with invasive fungal infections had Candida colonization.

The mean time to diagnosis was 70 days after transplantation. The most common etiologic agent for fungal infections was *Candida* albicans.

Conclusions: **Renal and liver recipients with *Candida* colonization are at high risk for fungal infections and therefore, control of fungal colonization in liver and renal transplant candidates would reduce the risk of invasive fungal infections after transplantation.**

Key words: *Kidney, liver, transplant, invasive fungal infections, candida colonization*

Fungal infections have been a major cause of morbidity and mortality after organ transplantation. They range from trivial (eg, mucocutaneous colonization) to life-threatening disseminated infections with multiorgan seeding. The prevalence of invasive fungal infections (IFIs) in solid organ transplant recipients ranges from 5% to 50% in kidney and liver recipients respectively. *Candida spp* and *Aspergillus spp* are responsible for more than 80% of all fungal infections in solid organ transplant recipients [1]. The incidence of fungal infections after renal transplantation ranges from 1%-14% depending on the hygiene and sanitation of the transplantation center [2, 3]. IFIs have been reported in 5%-42% of liver transplant recipients [4, 5]. IFIs are most commonly associated with secondary diagnoses of esophagitis, pneumonia, meningitis, and urinary tract infection. Most fungal infections will occur in the first 6 months after transplantation because of the use of numerous immunosuppression drugs [6]. Delay in diagnosis or treatment of IFIs may lead to high mortality.

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Since no reports exist about fungal infections in kidney and liver transplanted patients in Iran, this study was designed to evaluate the incidence, identify the most common fungal pathogens, and determine the associated risk factors in patients who had been transplanted and followed in the transplantation unit of Nemazi Hospital at the Shiraz University of Medical Sciences in Shiraz, Iran.

Materials and Methods

One hundred twenty renal (51 cadaver and 69 living donors) and 50 liver (cadaver donors) recipients were transplanted at the organ transplant unit of Nemazi Hospital in Shiraz, Iran, from 2004 to 2005, and were followed for fungal infections for at least 6 months. Renal transplant recipients (RTRs) did not receive any antifungal prophylaxis, but liver transplant recipients (LTRs) received fluconazole (400 mg/day) for 21 days after transplantation. Liver recipients received prednisolone, cyclosporin A, and tacrolimus, while kidney recipients received triple therapy consisting of prednisolone, cyclosporin A, and azathioprine. None of them received antilymphocytic therapy.

On admission to the hospital, all patients were evaluated for fungal colonization. Mouth, vaginal, and rectal swabs were examined microscopically and were cultured in Sabouraud dextrose agar (Merck, Darmstadt, Germany). Midstream urine samples were centrifuged for 10 minutes at 2500 rpm and then cultured. Colonization was considered in asymptomatic patients with negative smears (from mouth, vagina, rectum, urine) and positive cultures, while *infection* was diagnosed in symptomatic patients with positive smear and culture results. During follow-up, whenever the clinician detected the signs of infection, laboratory tests (urine, cerebrospinal fluid [CSF], pleural and abdominal tap, and 3 sputum samples) for the diagnosis of fungal infection were done.

Cutaneous mycosis was characterized by the damage caused by proliferation of fungi in the keratinized tissues of hair, nail, and skin. To obtain the cutaneous specimens, skin surrounding the lesion was cleaned with alcohol, and the edge of the lesion was scraped for microscopic examination and culture. To detect ear infection, after consultation with the otolaryngologist, a sample of pus was used for lab tests.

After specific processing of the samples, direct microscopic examination was performed for all specimens, using an India ink preparation for CSF and a potassium hydroxide preparation for all of the samples. Subsequently, all samples were cultured on Sabouraud dextrose agar with and without chloramphenicol.

Fungal cultures were incubated at 30ºC for at least 4 weeks. Plates were evaluated daily for the first 7 days and at least twice per week thereafter. Blood samples were cultured using the bedside inoculation method into an automated blood culture system (BACTEC system, Becton-Dickinson, Sparkes, Md, USA) from those patients who had fever during their hospital stay.

Fungal infections in these recipients were evaluated on the basis of their clinical presentation, microbiologic and histopathologic findings, clinical course, and response to antifungal therapy. Diagnosis of IFIs was made in the presence of at least 1 of the following criteria [7-9]:

1. Histopathologic evidence of tissue invasion on tissue biopsy
2. Positive culture from a deep tissue specimen such as blood, CSF, peritoneal fluid, or biopsy specimen
3. Positive cultures from ≥ 3 sites (BAL, urine, wound, etc)
4. At least 3 positive sputum smears for pseudohyphae and budding yeast and/or positive sputum culture with clinical findings consistent with pneumonitis resistant to broad-spectrum antibiotics

Positive smears and cultures, in the presence of clinical and radiographic signs, were considered as true, and in the absence of such signs were considered as false positive. Statistical analyses were done using SPSS software (Statistical Package for the Social Sciences, version 11.5, SSPS Inc, Chicago, Ill, USA). Fisher's exact test was used for the statistical analyses.

Results

One hundred seventy solid organ transplants were performed at Nemazi Hospital in Shiraz, Iran, between September 2004 and August 2005. Fifty-four kidney recipients (45%) and 42 liver recipients (84%) had *Candida* colonization in different sites of their bodies (Table 1).

In kidney transplant recipients, the female-to-male ratio was 53:67, and the mean age of recipients was 35.2 years (range, 4-73 years). Fungal infections were diagnosed in 13 of 120 (10.8%) RTRs. Eight patients had cutaneous and mucocutaneous infections: tinea

Table 1. Body sites colonized with *Candida spp*

Site of isolate	Kidney recipients		Liver recipients	
	Frequency (n)	(%)	Frequency (n)	(%)
Mouth	37	30.9	22	44.0
Vagina	6	5.0	---	---
Urine	1	0.8	---	---
Mouth/vagina	9	7.5	13	26.0
Mouth/rectal swab	1	0.8	7	14.0
Without colonization	66	55.0	8	16.0
Total	120	100.0	50	100.0

versicolor (4 patients), thrush (2 patients), perlèche (1 patient), and otomycosis (1 patient). The etiologic agents were *Candida albicans*, *Malassezia furfur*, and *Aspergillus niger*. IFIs occurred in 5 recipients (3 fungal pneumonitis and 2 severe esophagitis). Two of the infected renal recipients had received kidney from living donors, and 3 of them had received kidney from cadavers. All of the recipients with IFIs had been colonized with *Candida*, and 2 of them died.

In liver transplant recipients, the female-to-male ratio was 22:28, and the mean age of the recipients was 35.1 years (range, 3-57 years). Fungal infections were diagnosed in 6 of the recipients. Two recipients had mucocutaneous infections (1 perlèche and 1 vaginal candidiasis), and IFIs occurred in 4 liver transplant recipients (2 fungal pneumonitis, 1 meningitis, and 1 severe esophagitis). Three recipients with IFIs were colonized with *Candida spp* (Table 2).

The mean time for diagnosis was 70 days after transplantation (range, 14 days to 5 months). None of the patients with IFIs had a positive blood culture results. Lungs were the most common site of involvement. Five patients had pathologic findings on their chest radiographs. In 3 patients, infection was proven by endoscopy and a biopsy specimen from the esophagus. Eight patients with IFIs had

Table 2. Features of patients with cutaneous infections

Patient No. (kind of transplant)	Age (y) sex	Site	Pathogen	Time of fungal infections after transplantation
1 (liver)	32/F	tongue	*C. albicans*	8 months
2 (liver)	44/F	vagina	*C. albicans*	6 months
3 (kidney)	34/M	arm	*M. furfur*	3 months
4 (kidney)	16/F	neck	*M. furfur*	2 months
5 (kidney)	30/F	neck	*M. furfur*	4 months
6 (kidney)	33/F	arm	*M. furfur*	1.5 months
7 (kidney)	26/F	tongue	*C. albicans*	1.5 months
8 (kidney)	73/M	tongue	*C. albicans*	1 month
9 (kidney)	35/M	ear	*A. niger*	1 month
10 (kidney)	45/F	lips	*C. albicans*	2 weeks

C: Candida, M: Malassezia, A: Aspergillus

colonization in their mouth, and 6 female patients had colonization of *Candida albicans* in their mouth and vagina. One case of meningitis was observed in a liver transplant recipient who was a drug abuser, 3 patients were diabetic, and 1 patient had systemic lupus erythematosus. Two patients had both cutaneous and systemic fungal infections. The etiologic agents in IFIs were *Candida albicans* and *Aspergillus spp*. Five patients with IFIs (55.5%) died, and the others were treated with fluconazole and amphotericin B (Table 3).

Discussion

Cutaneous lesions can cause significant problems in solid organ transplant recipients, who are predisposed to superficial fungal infections because of immunosuppressive therapy. Cutaneous mycoses include dermatophytosis (ring worm), candidiasis (thrush), and pityriasis (tinea) versicolor. Other

Table 3. Features of patients with IFIs

Patient No. (kind of recipient)	Age (y) Sex	Site	Pathogen	Time of fungal infections after transplantation	Site of colonization	Outcome
1 (liver)	48/M	GI	*C. albicans*	21 days	mouth	died
2 (liver)	32/F	lung	*C. albicans*	1 month	mouth/vagina	remission
3 (liver)	44/M	lung	*C. albicans*	5 months	no colonization	died
4 (liver)	32/M	CNS	*Aspergillus spp*	3 months	mouth	died
5 (kidney)	24/F	lung	*C. albicans*	4 months	mouth/vagina	remission
6 (kidney)	46/F	GI	*C. albicans*	2 months	mouth/vagina	died
7 (kidney)	16/F	lung	*C. albicans*	2 months	mouth/vagina	remission
8 (kidney)	62/F	GI	*C. albicans*	3 months	mouth/vagina	died
9 (kidney)	54/F	lung	*C. albicans*	14 days	mouth/vagina	remission

C: Candida, IFI: invasive fungal infection, GI: gastrointestinal, CNS: central nervous system

epithelial surfaces that can be affected by superficial fungal infections are the external ear canal (otomycosis) and the cornea (keratomycosis) [10].

Gulec and coworkers have reported that 63.7% of the renal transplant recipients had cutaneous/oral candidiasis, dermatophytosis, or pityriasis versicolor [11]. Pityriasis versicolor (PV) is reported to be the most frequent dermatomycosis seen in renal transplant recipients in Italy [12]. In India, results of a 60-month study showed that of 117 mucocutaneous infections in renal recipients, 57 were viral, 49 were fungal, and 8 were bacterial, showing a high prevalence of fungal mucocutaneous infection in such patients. [13]. In our study, 6.6% of RTRs had cutaneous fungal infections, which differs from the above-cited results. This difference may be due to dry weather in Shiraz or short follow-up. In liver transplant recipients, the prevalence rate of mucocutaneous fungal infection was 4% in our study. *Candida albicans* was the most frequent agent causing mucocutaneous mycosis, and Tinea versicolor was the most frequent dermatomycosis.

IFI happens whenever the pathogen disseminates from one visceral organ to another. It has been reported that IFIs have significantly decreased (to 1%-2%) in developed countries during the last decade [14]. According to Dictar and coworkers, in Argentina, the prevalence rate of IFIs in RTRs was 3.5%, and in liver/liver-kidney recipients, the rate was 7.2% [1]. Chugh and colleagues have reported that after renal transplantation in India, 14% of the recipients had IFIs and suggested that this finding might be related to poor hygiene and sanitation [15]. In Turkey, the prevalence of IFIs was found to be 4% in 296 kidney transplant recipients [7]. In Kuwait, in a retrospective analysis, 18 of 512 (3.5%) renal transplant recipients had IFIs including candidiasis (8 patients), aspergillosis (5 patients), cryptococcosis (3 patients), and zygomycosis (2 patients) [16]. In our study, IFIs were seen in 8% of LTRs and 4% of RTRs. This is the first study in Iran about IFIs in transplant recipients. In Asian countries, no studies have been performed regarding the prevalence of fungal infections in liver transplant recipients until now. However, in renal transplant recipients, our results are similar with earlier reports.

It has been reported that intensive immunosuppression, long-term hospitalization, antibiotic consumption, and older age may be major predisposing factors for the high incidence of fungal infections [1, 2, 7, 14]. Recipients with coexisting diabetes mellitus are reported as being prone to fungal infections, particularly mucormycosis [7]. In our study, the mean age of patients with IFIs was 40 years, and the mean hospitalization periods were 14 and 40 days in RTRs and LTRs, respectively. There was a significant relation between colonization of *Candida* in mucosal tissues of the body (mouth, vagina) and fungal infection ($P = .01$). Among patients with IFIs, 88.9% had colonization with *Candida spp*. The female-to-male ratio for IFIs was 2 to 1. All women with IFIs also had *Candida* colonized in the mouth and vagina. We could not find any study showing a relation between fungal colonization in liver and renal recipients and IFIs. *Candida albicans* was the most frequent agent in our study. In other studies, *Candida* and *Aspergillus* were the most frequently isolated agents.

Conclusions

Renal and liver recipients with *Candida* colonization are at high risk for fungal infections; therefore, control of fungal colonization in liver and renal transplant candidates would reduce the risk of IFIs after transplantation.

References

1. Dictar MO, Maiolo E, Alexander B, Jacob N, Veron MT. Mycoses in the transplanted patient. Med Mycol 2000; 38: 251-258
2. Paya CV. Fungal infections in solid organ transplantation. Clin Infect Dis 1993; 16: 677-688
3. Chugh KS, Sakhuja V, Jain S, Talwar P, Minz M, Joshi K, et al. High mortality in systemic fungal infections following renal transplantation in third-world countries. Nephrol Dial Transplant 1993; 8: 168-172
4. Singh N, Gayowski T, Wagener MM, Doyle H, Marino IR. Invasive fungal infections in liver transplant recipients receiving tacrolimus as the primary immunosuppressive agent. Clin Infect Dis 1997; 24: 179-184
5. Briegel J, Forst H, Spill B, Haas A, Grabein B, Haller M, et al. Risk factors for systemic fungal infections in liver transplant recipients. Eur J Clin Microbiol Infect Dis 1995; 14: 375-382
6. Abbott KC, Hypolite I, Poropatich RK, Hshieh P, Cruess D, Hawkes CA, et al. Hospitalizations for fungal infections after renal transplantation in the United States. Transpl Infect Dis 2001; 3: 203-211
7. Altiparmak MR, Apaydin S, Trablus S, Serdengecti K, Ataman R, Ozturk R, et al. Systemic fungal infections after renal transplantation. Scand J Infect Dis 2002; 34: 284-288
8. Castaldo P, Stratta RJ, Wood RP, Markin RS, Patil KD, Shaefer MS, et al. Clinical spectrum of fungal infections after orthotopic liver transplantation. Arch Surg 1991; 126: 149-156
9. Horvath JA, Dummer S. The use of respiratory tract cultures in the diagnosis of invasive pulmonary aspergillosis. Am J Med 1991; 100: 171-178
10. Anaissie EJ, McGinnis MR, Pfaller MA (eds). Clinical Mycology, Philadelphia, Churchill Livingstone; 2003, p 456

11. Gulec AT, Demirbilek M, Seckin D, Can F, Saray Y, Sarifakioglu E, et al. Superficial fungal infections in 102 renal transplant recipients: a case-control study. J Am Acad Dermatol 2003; 49: 187-192
12. Virgili A, Zampino MR, La Malfa V, Strumia R, Bedani PL. Prevalence of superficial dermatomycoses in 73 renal transplant recipients. Dermatology 1999; 199: 31-34
13. Sandhu K, Gupta S, Kumar B, Dhandha R, Udigiri NK, Minz M. The pattern of mucocutaneous infections and infestations in renal transplant recipients. J Dermatol 2003; 30: 590-595
14. Snydman DR. Infection in solid organ transplantation. Transpl Infect Dis 1999; 1: 21-28
15. Chugh KS, Sakhuja V, Jain S, Talwar P, Minz M, Joshi K, et al. High
mortality in systemic fungal infections following renal transplantation in third-world countries. Nephrol Dial Transplant 1993; 8: 168-172
16. Nampoory MR, Khan ZU, Johny KV, Constandi JN, Gupta RK, Al-Muzairi I, et al. Invasive fungal infections in renal transplant recipients. J Infect 1996; 33: 95-101