Curr Fungal Infect Rep (2015) 9:57–64
DOI 10.1007/s12281-015-0217-2

PEDIATRIC FUNGAL INFECTIONS (T LEHRNBECHER, SECTION EDITOR)

Invasive Fungal Infections in Pediatric Solid Organ Transplant Patients: Epidemiology and Management

Aspasia Katragkou · Thomas J. Walsh · Emmanuel Roilides

Published online: 17 March 2015

Abstract Invasive fungal infections are important causes of morbidity and mortality in pediatric patients undergoing solid organ transplantation (SOT). Invasive candidiasis, cryptococcosis, and mold infections such as aspergillosis and mucormycosis are among the most prevalent fungal infections in this population. Invasive candidiasis is more common in high-risk liver transplantation as well as of pancreas and small bowel. Invasive aspergillosis is more frequent in transplantation of lungs followed by heart and liver. Invasive fungal infections constitute an important barrier to short- and long-term survival of the allograft and patient. Advances in pediatric infectious diseases supportive care have contributed substantially to the improved survival, outcome, and reduction of suffering caused by these infectious complications. The current prophylactic and treatment strategies vary widely in transplantation centers given the lack of clinical trials and scant epidemiological data in pediatric SOT recipients.

Keywords *Candida* · *Aspergillus* · Transplantation · *Pneumocystis jirovecii* · *Mucorales*

This article is part of the Topical Collection on *Pediatric Fungal Infections*

A. Katragkou · T. J. Walsh
Transplantation-Oncology Infectious Diseases Program, Weill Cornell Medical Center of Cornell University, New York, NY, USA

T. J. Walsh
Department of Pediatrics and Department of Microbiology and Immunology, Weill Cornell Medical College of Cornell University, New York, NY, USA

E. Roilides (✉)
Infectious Disease Unit, 3rd Department of Pediatrics, Faculty of Medicine, Aristotle University School of Health Sciences, Hippokration Hospital, Konstantinoupoleos 49, 546 42 Thessaloniki, Greece
e-mail: roilides@med.auth.gr

Introduction

Infectious diseases are major causes of morbidity and mortality in pediatric patients undergoing transplantation. They also represent the most significant barrier to short- and long-term survival of the transplant. Advances in pediatric infectious diseases supportive care have resulted in the ability of patients to undergo intensive immunosuppression and aggressive invasive procedures. The achievements during the past 30 years have resulted in remarkably improved outcome for pediatric transplant recipients. These advances of pediatric infectious disease supportive care have contributed substantially to the improved survival, outcome, and reduction of suffering to infectious complications.

This article reviews the epidemiology and strategies for managing infectious diseases in pediatric solid organ transplant patients. Because the immune defects and the possible etiologic agents of infection vary during the time elapsed since transplantation, the chapter is organized in such a manner. Timetables of infection after solid organ transplantation are useful as they facilitate differential diagnosis, infection control, prophylaxis, and treatment (Fig. 1). Definitive recommendations for prevention and treatment of invasive fungal infections in pediatric patients undergoing solid organ transplantation do not exist given the lack of clinical trials and scant epidemiological data.

Pediatric Versus Adult Patients

Pediatric transplant patients are different from their adult counterparts in multiple ways. These include the spectrum of underlying diseases requiring transplantation (i.e., cause of liver transplantation in adults is usually cirrhosis due to hepatitis; whereas in children, it is congenital atresia of bile ducts), the intensity of immunosuppressive regimens, and the

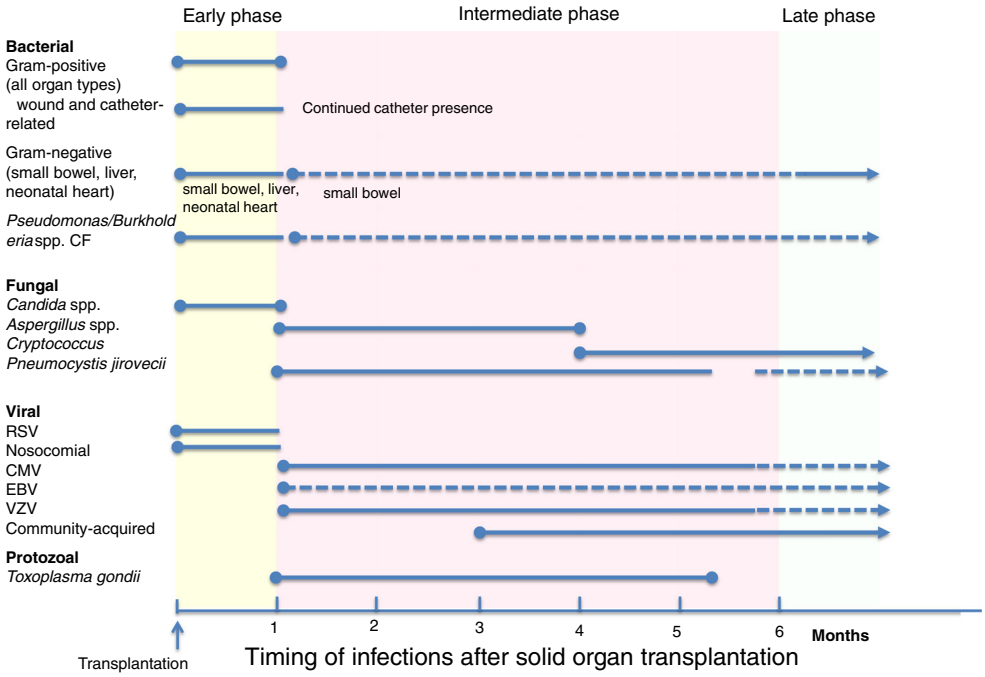

Fig. 1 Timetable of infections after solid organ transplantation in children. *Solid lines* indicate higher frequency of infections; *dashed lines* indicate lower frequency of infections. Modified with permission from [1]

incidence and severity of co-morbid medical conditions preceding the transplantation. In addition, the percentage of patients with indwelling central venous catheters, the community exposures to infectious pathogens, and the maturation of the immune system may differ in different ages. Diagnostic and therapeutic issues also are different between adults and children. Notably, a risk stratification system widely evaluated or clinically adopted in pediatrics is missing. Important surrogate markers for infection have not been validated in children (like (1–3)-β-D-glucan testing that has not been validated in children), while many antimicrobial agents lack pediatric approval or rigorous pediatric dosing and safety data. Lastly, a number of family/psychosocial issues are remarkably different between adults and children [2, 3].

Invasive Fungal Infections in Solid Organ Transplantation

Solid organ transplantation (SOT) is a major therapeutic option for many children with end-stage organ failure. For a successful SOT, a careful balance between rejection and infection should be attained. The risk of infection in the SOT recipients is determined by the interaction of multiple factors related to the recipient, the transplantation procedure, and the net state of immunosuppression occurring from the pre-transplantation until post-transplantation period (Table 1) [2, 4]. Infections in SOT recipients follow a temporal trend and tend to be predictable. While it would be over-simplistic to suggest that specific infections occur only at specific time points, it is nevertheless helpful to divide the period following transplantation into specific phases. In each phase, specific organisms predominate; however, infectious disease syndromes such as pneumonia can occur at any time in the post-transplant period but the etiology changes at different points in time. The timing of infections can be divided into three intervals: early (0–30 days after transplantation), intermediate (30–180 days after transplantation), and late (>180 days after transplantation) (Fig. 1) [1].

Early Phase Infections (0–30 Days After Transplantation)

The net state of immunosuppression at this phase is not great despite the high doses of immunosuppressive therapy. Thus, opportunistic infections (caused by pathogens such as *Aspergillus*, *Listeria*, and *Nocardia*) are rare. There are three types of infections during this period: (1) infections present to the recipient before transplantation, which are exacerbated after the transplantation due to the operation or immunosuppression; (2) donor-derived infections which are usually due to critical care, terminal illness, transport, implantation of the organ, or donor's undiagnosed infections (West Nile virus, HIV, rabies) [5–7] as well as undiagnosed critical care-related multi-resistant bacteria, such as *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*; and (3) infections transmitted perioperatively that could occur in an immunocompetent patient including *Candida* spp. The majority of the infections, during the early phase after transplantation is of this last type and is determined by the technical integrity of the surgery and the post-surgery use of indwelling medical devices. Early graft injuries (e.g., ischemia of bile

Table 1 Factors increasing the risk for infections in solid organ transplant recipients

Pre-transplantation factors	Peri-transplantation factors	Post-transplantation factors
- Young age - Underlying disease - Duration and frequency of hospitalizations - Surgery before transplantation - Complications of end-stage organ disease - Malnutrition - Environmental exposures (community, hospitals) - Travel	- Type of organ transplanted (cadaveric or alive donor; kidney or liver or lungs, etc.) - Donor-derived infections - Transplant procedure (injury, prolonged time, technical problems) - Indwelling medical devices	- Net state of immunosuppression • Dose, duration, and temporal sequence of immunosuppressive agents (steroids, calcineurin inhibitors, sirolimus) • Rejection and its treatment (antithymocyte globulin, alemtuzumab, balivizumab) • Host defense defects due to underlying disease • Technical/anatomic abnormalities that compromise the integrity of mucocutaneous barriers • Neutropenia • Metabolic abnormalities (protein-calorie malnutrition, uremia, hyperglycemia) • Viral infections with immunomodulating effect (CMV, EBV, HBV, HCV, HIV) - Environmental exposure (community, hospital) - Indwelling medical devices

ducts or pulmonary reperfusion injury) may later become foci of liver or lung abscesses [8•].

Intermediate Phase Infections (30–180 Days After Transplantation)

The infections occurring in this phase are the result of immunosuppression and the immunomodulatory effects of co-infecting viruses. There are three types of infections during this period: (1) the remaining infections from the previous phase and (2) viral infections most commonly due to CMV, Epstein-Barr virus (EBV), Herpesvirus-6, Hepatitis B and C, and HIV. However, other rare viral pathogens such as polyomavirus BK and adenovirus have emerged and (3) opportunistic infections due to *Pneumocystis jirovecii* and *Aspergillus fumigatus*, which usually suggest an environmental source. Additionally, infections due to endemic fungi like *Cryptococcus neoformans* or infections due to *Trypanosoma cruzi* or *Strongyloides stercoralis* may occur [2, 9].

Late Phase Infections (More than 6 Months After Transplantation)

There are three types of infections during this period: (1) patients with good transplantation outcome (minimal immunosuppression, good allograft function, no viral infections) are at risk from infection due to community-acquired respiratory viruses (influenza, parainfluenza and respiratory syncytial virus); (2) patients with chronic viral infections that may cause allograft injury (cirrhosis from HCV infection in liver transplant recipients, bronchiolitis obliterans in lung transplant recipients, accelerated vasculopathy in heart transplant recipients with CMV infection) or a malignant condition such as post-transplantation lymphoproliferative disorder (PTLD) or skin or anogenital cancer and (3) patients with poor result from transplantation (repeated episodes of acute and chronic allograft injury, excessive immunosuppression, and chronic viral infections). These patients are at risk for opportunistic infections with *Listeria monocytogenes* or *Nocardia* species and invasive fungal infections such as *Mucorales* and dematiaceous molds and unusual organisms (e.g., *Rhodococcus* species) [2, 8•, 9, 10].

The most common invasive fungal infections in this population are candidiasis and mold infections such aspergillosis and mucormycosis, followed by cryptococcosis [11•, 12–22]. *Candida* spp. are the most frequent agents of invasive fungal infections accounting for around 2–4 % of SOT [11•, 23, 24]. The incidences vary according to the transplantation center and organ transplanted being particularly high in abdominal SOT such as intestinal, pancreas, and liver transplantation [11•] and uncommon in heart, lung, or kidney transplantations [25]. The majority of candidiasis cases after SOT occur during the first months after surgery [26•]. The main risk factors for invasive candidiasis are receipt of broad-spectrum antibiotics, presence of central venous catheters, complicated operative courses (re-transplantation, anastomotic problems, laparotomy after transplantation), vascular thrombosis, multifocal colonization, receipt of parenteral nutrition, and hyperglycemia [26•, 27–29]. Mortality of invasive candidiasis in 12 months has been reported in the Transplant-Associated Infection Surveillance Network (TRANSNET) study of predominantly adult patients to be 34 % [11•].

The incidence of invasive aspergillosis varies from 0.1 to 3.5 % depending on the transplantation center and type of transplant. The highest risk for aspergillosis occurs among lung transplant recipients [30••, 31, 32••, 33]. In these patients, colonization of the transplanted lung with *Aspergillus* spp., bronchial anastomotic ischemia or bronchial stent placement, hypogammaglobulinemia, concomitant CMV pneumonia, and cystic fibrosis are among the most prominent risk factors

for development of invasive aspergillosis [34–38]. Mortality of invasive aspergillosis in SOT recipients who develop invasive pulmonary disease also depends on the type of transplant; it has been reported to be 29.4 % in adult patients with heart-lung transplantation [39], 41 % in TRANSNET study of predominantly adult patients [11•], and 9.5–47.1 % depending on the transplant type in adults [40].

The incidence of cryptococcosis varies from 0 to 1.5 % according to the SOT series making *C. neoformans* the third leading cause of invasive fungal infections among SOT recipients [11•, 26•]. The rates are higher in kidney and heart transplant recipients [26•]. The most prevalent risk factors are treatment with high dose of corticosteroids or monoclonal antibodies against lymphocytes or tumor necrosis factor (alemtuzumab and infliximab) [41]. The majority of cryptococcosis cases occur late after transplantation, usually after 16 to 21 months [26•]. Mortality of cryptococcosis after SOT is reported to be 14 to 27 % in adults [11•, 42].

Management

Treatment of invasive candidiasis in SOT recipients is similar with that of non-neutropenic patients. According to the last recommendations of the ESCMID Study Group for infections in Compromised Hosts (ESGICH), where there is a special mention for children, the use of an echinocandin (caspofungin or micafungin) is strongly recommended for initial treatment of non-neutropenic transplant recipients. Another option is liposomal amphotericin B; whereas, fluconazole constitutes a second-line alternative as certain *Candida* spp. may be fluconazole resistant and drug-drug interactions exist with calcineurin inhibitors [26•]. Duration of treatment is recommended to be 14 days for uncomplicated candidemia while prolongation of treatment should be considered in complicated infections. Once the patient is stable, can tolerate oral administration, is known to have a fluconazole-susceptible *Candida* sp., and has completed 10 days of intravenous antifungal therapy, conversion to oral fluconazole can be considered [26•].

Catheter-Associated Candidemia Removal of chronic indwelling central venous catheters is best determined by the type of organism recovered, the hemodynamic stability of the patient, and the presence of persistent bacteremia, rather than by differences in colony counts suggesting evidence of direct involvement of the catheter. Removal and replacement of chronic indwelling catheters carries the risk of general anesthesia, pneumothorax, and hemorrhage, particularly in thrombocytopenic patients. This measure has been associated with lower mortality in neonates and non-neutropenic patients in whom the vascular catheter, rather than the GI tract, is considered to be the source of candidemia [43, 44].

The basic principles of therapy for invasive aspergillosis in SOT recipients include the prompt initiation of antifungal therapy and the individualization of treatment according to type of transplant, type of infection, and immunosuppression state. A key point in the treatment of invasive aspergillosis in SOT recipients is the reduction of immunosuppression, especially of corticosteroids, whenever possible. First-line treatment is with voriconazole. However, in patients where the use of voriconazole is contraindicated (i.e., age less than 2 years, renal insufficiency prohibiting use of intravenous voriconazole), liposomal amphotericin B is recommended. Combination antifungal treatment (voriconazole or amphotericin B plus caspofungin) may be considered in pediatric patients with severe disease. The optimum duration of treatment has not been established; it is recommended to be continued until clinical and radiological responses (minimum 6–12 weeks) [26•]. On many occasions, surgical debridement is required as an adjunct to effective antifungal treatment [26•, 37].

In contrast to recommendations for adult SOT patients [26•, 45], no established guidelines exist for the pediatric population (Table 2).

Prevention of Infections

General Measures The most effective and practical intervention by which to prevent or reduce infections in the immunocompromised host is adherence to strict hand washing practices [46]. A restricted (cooked) diet has not been proven to be beneficial in avoiding infection in immunocompromised patients, as previously believed [47].

Environmental sources may contribute to fungal (especially *Aspergillus* spp., *Fusarium* spp., and *Mucorales*) colonization and infection. In medical centers where *Aspergillus* spp. and *Fusarium* spp. are a significant problem, special air filtration systems, such as high-efficiency particulate air filters (HEPA filters), and close attention to cleaning bathroom facilities as well as avoiding construction areas and other sources of molds at home may be helpful [48, 49].

Total protective isolation is a comprehensive regimen designed to reduce patients' endogenous microbiota while preventing the acquisition of new organisms. A sterile environment is created in a clean-air room with constant positive-pressure airflow. It is maintained by an aggressive program of surface decontamination and sterilization of all objects that enter the room and by an intensive regimen to disinfect the patient, including oral non-absorbable antibiotics, skin antiseptics, antibiotic sprays, and ointments and a low-microbial diet. The total protective environment reduces the number of infections in profoundly neutropenic patients. However, a total protective environment is expensive, and because of the improvement in

Table 2 Antifungal agents used in children for infections after solid organ transplantation

Class	Agent	Route	Spectrum	Daily dose (maximum)		Comments
				Infants (31 days–1 year)	Children (>1–17 years)	
Polyenes	Deoxycholate amphotericin B	IV	Very broad antifungal activity including *Candida* spp., *Aspergillus* spp., *Mucorales*, *Cryptococcus neoformans*, and *Histoplasma capsulatum*	Empirical therapy: 0.5–1.5 mg/kg Q24h Documented fungal infections: 1.0–1.5 mg/kg Q24h		Children can generally tolerate higher doses than adults
	Lipid formulations (amphotericin B lipid complex, and liposomal amphotericin B)	IV	Same spectrum as deoxycholate formulation	Empirical therapy: 3 mg/kg Q24h Documented fungal infections: 5 mg/kg Q24h (max dose 10 mg/kg, but no evidence for improved efficacy)		Significantly less nephrotoxicity with efficacy at least equal to that of deoxycholate amphotericin B
Triazoles	Fluconazole	PO, IV	*Candida* spp. (not *C. krusei* and not some strains of *C. glabrata*), *C. neoformans*, *Trichosporon* spp., and *Coccidioides immitis*	12 mg/kg Q24h	3–12 mg/kg Q24h Life-threatening infections: 12 mg/kg/day Q12h (max 600 mg/day)	Excellent bioavailability, independent of gastric acidity Higher dose required in children and infants due to shorter half-life
	Itraconazole	PO, IV	*Aspergillus* spp., *Candida* spp., *H. capsulatum*, *Blastomyces dermatitidis*, and *C. immitis*	Unknown	Load with 6 mg/kg/day Q12h × 1 day; maintain with 2.5–5 mg/kg/day Q12h (max 10 mg/kg/day)[a]	Absorption erratic but increased with taking drug with meals or by using cyclodextrin formulation Dosing Q12h preferred in children TDM recommended
	Voriconazole	PO, IV	*Candida* spp., *Aspergillus* spp., *Trichosporon* spp. and some strains of *Scedosporium* spp., and *Fusarium* spp.		Day 1: 9 mg/kg Q12h, then 8 mg/kg Q12h iv; and 9 mg/kg Q12h for oral administration (max 350 mg Q12h) for 2–14 years and approved adult dose for patients ≥15 years and 12–14 years weighing >50 kg PO, <40 kg: 200 mg Q12h then 100 mg Q12h >40 kg: 400 mg Q12h, then 200 mg Q12h	Pediatric suspension is available; bioavailability is reliable and is enhanced with empty stomach TDM recommended Voriconazole is approved for children >2 years.
	Posaconazole	PO	*Mucorales*, *Candida* spp., and *Aspergillus* spp.	Unknown	Prophylaxis: 600 mg/day Q8h Therapy: 800 mg orally Q6 or Q12h	TDM recommended For children aged ≥13 years
Echinocandins	Caspofungin	IV	*Candida* spp. and *Aspergillus* spp.	50 mg/m^2 Q24h	Load with 70 mg/m^2/day for 1 day; maintain with 50 mg/m^2/day Q24h (max 70 mg)	Dosing should be adjusted for hepatic insufficiency to 35 mg/m^2 Q24h
	Micafungin	IV	Similar spectrum	2–4 mg/kg iv once daily	2–4 mg/kg iv once daily (children weighing ≥50 kg: 100–200 mg)	Not licensed in the USA for children

TDM therapeutic drug monitoring

[a] IV formulation for itraconazole is available but dosage and pharmacokinetics have not been defined in pediatric patients

treating established infections, it does not offer a survival advantage to SOT patients. Total protective isolation is not necessary for the routine care of immunosuppressed patients [50].

Antifungal Prophylaxis Given the lack of clinical trials and the scant epidemiological data, there are no definitive recommendations for the use of prophylaxis against invasive fungal infections in children with SOT. The selection of universal versus targeted prophylaxis is based on the type of transplant. In addition, the choice of prophylaxis is based on the effectiveness, side effects, and drug interactions of the antifungal agents with the concomitant agents [26•, 51]. The general trend is not to use universal prophylaxis for *Candida* spp. infection in renal, heart, and lung transplantation while there is a well-established practice to use antifungal prophylaxis in patients undergoing high-risk liver, intestinal, or pancreatic transplantation [26•, 52]. On the contrary, it is common to use universal prophylaxis against *Aspergillus* in lung transplant recipients given the high morbidity and mortality rates of invasive infection [26•]. However, there is variability on the prophylaxis strategies according to the transplantation program [53].

Fluconazole is recommended for prevention of deep invasive fungal infections in immunocompromised patients when the risk of aspergillosis is not high. Randomized controlled studies have established fluconazole as good as other antifungals for prevention of invasive candidiasis in liver transplant recipients [54, 55]. However, the shift in the colonization pattern towards more resistant species, including *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, *Aspergillus* spp., and other filamentous fungi, is of concern [56, 57]. In a recently published randomized clinical trial comparing 100 mg micafungin with standard care antifungal prophylaxis (predefined for each participating institution to be either fluconazole or liposomal amphotericin B or caspofungin) in high-risk liver transplant adult patients, micafungin was noninferior and had a better kidney safety profile [58].

Pneumocystis Prophylaxis There are several effective regimens for *P. jirovecii* pneumonia (PCP) prophylaxis. The choice among them often depends on the patient's tolerance of their various side effects. Trimethoprim-sulfamethoxazole (TMP-SMX), given twice a day for 3 days a week, is considered the first-line regimen [59]. For patients who can tolerate this regimen, protection against PCP is virtually complete [60]. The use of TMP-SMX is limited, however, in a significant number of individuals by rash, neutropenia, and gastrointestinal symptoms. Alternative compounds for prevention of PCP in patients who are intolerant of or refractory to TMP-SMX include dapsone, atovaquone, and aerosolized pentamidine.

In conclusion, the current prophylactic and treatment strategies for solid organ transplantation in children vary widely among transplantation centers given the lack of clinical trials and scant epidemiological data in pediatric SOT recipients. There is an urgent need for future epidemiological, diagnostic, and management studies in this growing field of medicine.

Compliance with Ethics Guidelines

Conflict of Interest A Katragkou, TJ Walsh, and E Roilides all declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Marty FM, Rubin RH. The prevention of infection post-transplant: the role of prophylaxis, preemptive and empiric therapy. Transpl Int. 2006;19:2–11.
2. Fonseca-Aten M, Michaels MG. Infections in pediatric solid organ transplant recipients. Semin Pediatr Surg. 2006;15:153–61.
3. Sung L, Phillips R, Lehrnbecher T. Time for paediatric febrile neutropenia guidelines—children are not little adults. Eur J Cancer. 2011;47:811–3.
4. Rubin RH, Ikonen T, Gummert JF, Morris RE. The therapeutic prescription for the organ transplant recipient: the linkage of immunosuppression and antimicrobial strategies. Transpl Infect Dis. 1999;1:29–39.
5. Gottesdiener KM. Transplanted infections: donor-to-host transmission with the allograft. Ann Intern Med. 1989;110:1001–16.
6. Iwamoto M, Jernigan DB, Guasch A, et al. Transmission of West Nile virus from an organ donor to four transplant recipients. N Engl J Med. 2003;348:2196–203.
7. Srinivasan A, Burton EC, Kuehnert MJ, et al. Transmission of rabies virus from an organ donor to four transplant recipients. N Engl J Med. 2005;352:1103–11.
8. • Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med. 2007;357:2601–14. *This review summurizes the general conepts in the management of transplantation-associated infections and discusses advances and challenges*.
9. Allen U, Green M. Prevention and treatment of infectious complications after solid organ transplantation in children. Pediatr Clin N Am. 2010;57:459–79. *table of contents*.
10. Keough WL, Michaels MG. Infectious complications in pediatric solid organ transplantation. Pediatr Clin N Am. 2003;50:1451–69.
11. • Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis. 2010;50:1101–11. *The report of the results of a 5 year prospective study from 15 TRANSNET centers, representing a large and geographically diverse surveillance study focusing on post-transplant invasive fungal infections*.
12. Patel R. Infections in recipients of kidney transplants. Infect Dis Clin N Am. 2001;15:901–52.

13. Silveira FP, Husain S. Fungal infections in solid organ transplantation. Med Mycol. 2007;45:305–20.
14. Singh N. Fungal infections in the recipients of solid organ transplantation. Infect Dis Clin N Am. 2003;17:113–34.
15. Paya CV. Fungal infections in solid-organ transplantation. Clin Infect Dis. 1993;16:677–88.
16. Hadley S, Karchmer AW. Fungal infections in solid organ transplant recipients. Infect Dis Clin N Am. 1995;9:1045–74.
17. Stelzmueller I, Lass-Floerl C, Geltner C, et al. Zygomycosis and other rare filamentous fungal infections in solid organ transplant recipients. Transpl Int. 2008;21:534–46.
18. Minari A, Husni R, Avery RK, et al. The incidence of invasive aspergillosis among solid organ transplant recipients and implications for prophylaxis in lung transplants. Transpl Infect Dis. 2002;4:195–200.
19. Patterson JE, Peters J, Calhoon JH, et al. Investigation and control of aspergillosis and other filamentous fungal infections in solid organ transplant recipients. Transpl Infect Dis. 2000;2:22–8.
20. Trullas JC, Cervera C, Benito N, et al. Invasive pulmonary aspergillosis in solid organ and bone marrow transplant recipients. Transplant Proc. 2005;37:4091–3.
21. Iversen M, Burton CM, Vand S, et al. Aspergillus infection in lung transplant patients: incidence and prognosis. Eur J Clin Microbiol Infect Dis. 2007;26:879–86.
22. Vilchez R, Shapiro R, McCurry K, et al. Longitudinal study of cryptococcosis in adult solid-organ transplant recipients. Transpl Int. 2003;16:336–40.
23. Moreno A, Cervera C, Gavalda J, et al. Bloodstream infections among transplant recipients: results of a nationwide surveillance in Spain. Am J Transplant. 2007;7:2579–86.
24. Nafady-Hego H, Elgendy H, Moghazy WE, Fukuda K, Uemoto S. Pattern of bacterial and fungal infections in the first 3 months after pediatric living donor liver transplantation: an 11-year single-center experience. Liver Transpl. 2011;17:976–84.
25. Rodriguez C, Munoz P, Rodriguez-Creixems M, et al. Bloodstream infections among heart transplant recipients. Transplantation. 2006;81:384–91.
26.• Gavalda J, Meije Y, Fortun J, et al. Invasive fungal infections in solid organ transplant recipients. Clin Microbiol Infect. 2014;20 Suppl 7:27–48. *The most comprehensive and updated review on invasive fungal infections in solid organ transplant recipients from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Infections in Compromised Hosts (ESGICH)*.
27. Nieto-Rodriguez JA, Kusne S, Manez R, et al. Factors associated with the development of candidemia and candidemia-related death among liver transplant recipients. Ann Surg. 1996;223:70–6.
28. Patel R, Portela D, Badley AD, et al. Risk factors of invasive Candida and non-Candida fungal infections after liver transplantation. Transplantation. 1996;62:926–34.
29. Husain S, Tollemar J, Dominguez EA, et al. Changes in the spectrum and risk factors for invasive candidiasis in liver transplant recipients: prospective, multicenter, case-controlled study. Transplantation. 2003;75:2023–9.
30.•• Gavalda J, Len O, San Juan R, et al. Risk factors for invasive aspergillosis in solid-organ transplant recipients: a case-control study. Clin Infect Dis. 2005;41:52–9. *A well-conducted epidemiological study. The authors concluded that different risk factors exist in patients with early-onset aspergillosis and those with late-onset aspergillosis*.
31. Lortholary O, Gangneux JP, Sitbon K, et al. Epidemiological trends in invasive aspergillosis in France: the SAIF network (2005–2007). Clin Microbiol Infect. 2011;17:1882–9.
32.•• Munoz P, Ceron I, Valerio M, et al. Invasive aspergillosis among heart transplant recipients: a 24-year perspective. J Heart Lung Transplant. 2014;33:278–88. *A large and comprehensive experience of invasive aspergillosis in heart transplant recipients. This large study showed that both incidence and mortality exhibited a decrease in recent years and outlines the importance of careful environmental management and targeted anti-fungal prophylaxis.*
33. Zaoutis TE, Heydon K, Chu JH, Walsh TJ, Steinbach WJ. Epidemiology, outcomes, and costs of invasive aspergillosis in immunocompromised children in the United States, 2000. Pediatrics. 2006;117:e711–6.
34. Goldfarb NS, Avery RK, Goormastic M, et al. Hypogammaglobulinemia in lung transplant recipients. Transplantation. 2001;71:242–6.
35. Husni RN, Gordon SM, Longworth DL, et al. Cytomegalovirus infection is a risk factor for invasive aspergillosis in lung transplant recipients. Clin Infect Dis. 1998;26:753–5.
36. Westney GE, Kesten S, De Hoyos A, et al. Aspergillus infection in single and double lung transplant recipients. Transplantation. 1996;61:915–9.
37. Shoham S, Marr KA. Invasive fungal infections in solid organ transplant recipients. Future Microbiol. 2012;7:639–55.
38. Liu M, Worley S, Mallory Jr GB, et al. Fungal infections in pediatric lung transplant recipients: colonization and invasive disease. J Heart Lung Transplant. 2009;28:1226–30.
39. Grossi P, Farina C, Fiocchi R, Dalla GD. Prevalence and outcome of invasive fungal infections in 1,963 thoracic organ transplant recipients: a multicenter retrospective study. Italian Study Group of Fungal Infections in Thoracic Organ Transplant Recipients. Transplantation. 2000;70:112–6.
40. Neofytos D, Treadway S, Ostrander D, et al. Epidemiology, outcomes, and mortality predictors of invasive mold infections among transplant recipients: a 10-year, single-center experience. Transpl Infect Dis. 2013;15:233–42.
41. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:291–322.
42. Singh N, Alexander BD, Lortholary O, et al. Cryptococcus neoformans in organ transplant recipients: impact of calcineurin-inhibitor agents on mortality. J Infect Dis. 2007;195:756–64.
43. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:503–35.
44. Liu CY, Huang LJ, Wang WS, et al. Candidemia in cancer patients: impact of early removal of non-tunneled central venous catheters on outcome. J Infect. 2009;58:154–60.
45. Cornely OA, Bassetti M, Calandra T, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect. 2012;18 Suppl 7:19–37.
46. Doebbeling BN, Stanley GL, Sheetz CT, et al. Comparative efficacy of alternative hand-washing agents in reducing nosocomial infections in intensive care units. N Engl J Med. 1992;327:88–93.
47. Jubelirer SJ. The benefit of the neutropenic diet: fact or fiction? Oncologist. 2011;16:704–7.
48. Anaissie EJ, Stratton SL, Dignani MC, et al. Cleaning patient shower facilities: a novel approach to reducing patient exposure to aerosolized Aspergillus species and other opportunistic molds. Clin Infect Dis. 2002;35:E86–8.
49. Walsh TJ, Dixon DM. Nosocomial aspergillosis: environmental microbiology, hospital epidemiology, diagnosis and treatment. Eur J Epidemiol. 1989;5:131–42.
50. Hayes-Lattin B, Leis JF, Maziarz RT. Isolation in the allogeneic transplant environment: how protective is it? Bone Marrow Transplant. 2005;36:373–81.

51. Mead L, Danziger-Isakov LA, Michaels MG, et al. Antifungal prophylaxis in pediatric lung transplantation: an international multicenter survey. Pediatr Transplant. 2014;18:393–7.
52. Guaraldi G, Cocchi S, Codeluppi M, et al. Outcome, incidence, and timing of infectious complications in small bowel and multivisceral organ transplantation patients. Transplantation. 2005;80:1742–8.
53. Husain S, Zaldonis D, Kusne S, et al. Variation in antifungal prophylaxis strategies in lung transplantation. Transpl Infect Dis. 2006;8:213–8.
54. Evans JD, Morris PJ, Knight SR. Antifungal prophylaxis in liver transplantation: a systematic review and network meta-analysis. Am J Transplant. 2014;14:2765–76.
55. Winston DJ, Limaye AP, Pelletier S, et al. Randomized, double-blind trial of anidulafungin versus fluconazole for prophylaxis of invasive fungal infections in high-risk liver transplant recipients. Am J Transplant. 2014;14:2758–64.
56. Walsh TJ, Groll A, Hiemenz J, et al. Infections due to emerging and uncommon medically important fungal pathogens. Clin Microbiol Infect. 2004;10 Suppl 1:48–66.
57. Perlroth J, Choi B, Spellberg B. Nosocomial fungal infections: epidemiology, diagnosis, and treatment. Med Mycol. 2007;45:321–46.
58. Saliba F, Pascher A, Cointault O, et al. Randomized trial of micafungin for the prevention of invasive fungal infection in high-risk liver transplant recipients. Clin Infect Dis. 2014
59. Hughes WT, Rivera GK, Schell MJ, Thornton D, Lott L. Successful intermittent chemoprophylaxis for Pneumocystis carinii pneumonitis. N Engl J Med. 1987;316:1627–32.
60. Ioannidis JP, Cappelleri JC, Skolnik PR, Lau J, Sacks HS. A meta-analysis of the relative efficacy and toxicity of Pneumocystis carinii prophylactic regimens. Arch Intern Med. 1996;156:177–88.