Fungal infections in transplant recipients: pros and cons of immunosuppressive and antimicrobial treatment

Nicolas Papon, Gilles Nevez, Solène Le Gal, Cécile Vigneau, Florence Robert-Gangneux, Jean-Philippe Bouchara, Oliver Cornely, David Denning, Jean-Pierre Gangneux

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The continuing increase in the number of patients treated with transplantation procedures is attested by a worldwide activity of more than 150 000 grafts per year, including solid-organ transplants and haematopoietic stem-cell transplants.[1,2] Recipients of solid-organ transplants or haematopoietic stem-cell transplants are exposed to various types of complications, including rejection (mainly graft-versus-host disease) and infectious diseases (especially bacterial, viral, and fungal infections, and occasionally protozoal infections). Invasive fungal infections are a major cause of morbidity and mortality in recipients of solid-organ transplants and haematopoietic stem-cell transplants.[3,4] On the basis of recent breakthroughs in medical mycology from both pathophysiological and epidemiological perspectives, now is the time to reflect on outstanding needs to guide future research in this domain.

Although one size does not fit all and risk assessment is imprecise at present, the typical transplant recipient receives multiple immunosuppressive and prophylaxis agents to prevent both organ or cell rejection and microbial infections (table). The adverse effects of the different molecules used, but above all the potential drug interactions which have an effect on pharmacokinetics, pharmacodynamics, and toxicity, can be deleterious factors for transplantation outcome. On the positive side, there is growing in-vitro evidence that some of these interactions result in synergistic antimicrobial effects.[3] On the negative side, emerging evidence shows that antifungal prophylaxis is linked to drug-resistant

	Pros	Cons
Immunosuppressive prophylaxis	Essential to avoid rejection of transplanted organs or cells. Calcineurin inhibitors (eg, tacrolimus and cyclosporin A), inhibitors of the mammalian target of rapamycin pathway (eg, sirolimus), or inhibitors of de novo biosynthesis of guanine nucleotides (eg, mycophenolic acid) possess intrinsic antifungal activity against selected fungi, including *Candida* spp, *Cryptococcus* spp, *Aspergillus* spp, Mucorales, and some dimorphic fungi. Combinations of immunosuppressive and antifungal agents are potentially synergistic.	Immunosuppression is conducive to life-threatening invasive fungal infections due to many opportunistic fungal species that otherwise behave as commensals in humans or as saprophytes in the environment. The antifungal activity of some immunosuppressive agents can lead to deleterious microbiota changes and to the selection of environmental species or isolates resistant to these drugs. Drug–drug interactions and genetic determinants of the patient might lead to suboptimal levels or drug accumulation and toxicity. Azoles combined with calcineurin (eg, tacrolimus and cyclosporin A) and mammalian target of rapamycin (eg, sirolimus and everolimus) inhibitors increase their toxicities (especially nephrotoxicity).
Antibacterial prophylaxis	Reduces the risk of bacteraemia. Some antibiotics have intrinsic antifungal activities against some fungal species (eg, cotrimoxazole, which is used for the prophylaxis of *Pneumocystis jirovecii*). Combinations of antifungals and antibiotics are potentially synergistic.	Antibiotics decrease bacterial and fungal diversity in the microbiota. This response could promote the expansion of commensal and colonising opportunistic fungal and bacterial species (especially *Candida* spp, *Cryptococcus* spp, *Pneumocystis* spp, *Aspergillus* spp, and multidrug-resistant bacteria), and thus potentially influences the development of invasive fungal infections. Some drug–drug interactions result in nephrotoxicity or hepatotoxicity, or both.
Antifungal prophylaxis	Decreases the incidence and mortality of invasive fungal infections. Reduces the need for empirical antifungal therapy. Has the potential to reduce obstructive bronchiolitis in lung transplant recipients. Combinations of antifungals and antibiotics are potentially synergistic.	Antifungal prophylaxis decreases fungal diversity in the microbiota. This response promotes infection with commensal and colonising opportunistic fungal species (particularly non-*albicans* species of *Candida* and Mucorales that are naturally less susceptible to some antifungals, azole-resistant *Aspergillus* spp, or breakthrough fungi that are resistant to antifungal treatment). Resistance is acquired under antifungal long-term prophylaxis (lung transplantation). Decreases the performance of breakthrough infection diagnostic tests. There are multiple drug–drug interactions.
Antiviral prophylaxis	Decreases incidence of viral infections, in particular, herpes simplex virus, varicella zoster virus, and cytomegalovirus. Probably decreases mortality from cytomegalovirus disease, and rejection episodes.	Drug toxicity is considerable. Occasional resistance in cytomegalovirus has been reported. There are some drug–drug interactions, but these interactions rarely lead to nephrotoxicity or hepatotoxicity.
Antiprotozoal prophylaxis	Cotrimoxazole prevents toxoplasmosis that is acquired in recipients of solid-organ transplantation (particularly in the case of mismatch between the seropositive organ donor and seronegative recipient) and the risk of toxoplasma reactivation in recipients of haematopoietic stem-cell transplants and solid-organ transplants (heart or liver) who are toxoplasma seropositive.	Some drug–drug interactions result in nephrotoxicity or hepatotoxicity, or both.

Table: **Pros and cons of prophylaxis for transplant recipients**

fungal infections in transplantation units.[6] This finding is particularly problematic in the context of human-to-human airborne transmitted fungal species (eg, *Pneumocystis jirovecii*).[6] Of concern, antibacterial, antitoxoplasma, and antifungal prophylactic regimens recommended for haematopoietic stem-cell transplants probably result in the disruption of the balance of the microbiota. This disruption to the microbiota has the potential to promote the selection of certain fungal isolates or species that are less susceptible to antifungal treatment, which can then invade the bloodstream and cause fatal invasive fungal infections.[7] The increase in antifungal resistance challenges current practice. Acquired resistance to antifungals (initially to azoles, but more recently to echinocandins),[8] changes in the epidemiology of fungal species most often involved (eg, increase in mucormycosis),[9] and also the emergence of new species (eg, *Candida auris*)[10] all need to be accommodated to optimise future prophylaxis and treatment choices.

One major direction for research is now to accurately assess the effect of current immunosuppressive regimens on the risk of developing specific invasive fungal infections, given their antifungal properties. The natural antifungal activity of immunosuppressants could alter the selection of particular isolates, clades, and species or promote the emergence of acquired resistance. For example, the widely used immunosuppressive mycophenolate mofetil, which is well documented for its marked antifungal action, could participate in the transplant process to destroy most of the commensal and intrusive fungal population, to the benefit of invading rare species or isolates resistant to mycophenolic acid (naturally or secondarily).[11] The use of mycophenolate mofetil treatment could contribute to the burden of invasive fungal infections in patients receiving kidney transplants.[12] If confirmed, molecular determinants of fungal resistance to immunosuppressants should be developed as rapid detection tools to predict clinical outcomes and to dynamically adjust prophylactic regimens during the transplantation process.

Recent advances, but also future research, should help to continue improving the therapeutic prophylaxis protocols currently recommended to minimise the risks of invasive fungal infections. Globally, these improvements could be based on better knowledge of the local ecology to identify the right drug for precisely the right situation, and on therapeutic drug monitoring and dose adjustment for targeted antifungal stewardship. Environmental prevention, in addition to chemoprophylaxis, should be envisaged where relevant. Efforts should be made to identify new classes of antimicrobials with less toxicity and drug–drug interactions but also to determine new routes of administration with reduced effects on the intestinal microbiota. Finally, new high-throughput or deep-sequencing strategies could be used in the near future as part of an early diagnosis of the microbiota destabilisation.[7] All of these aspects should be taken into account and would represent further steps towards a personalised approach to prophylaxis in patients receiving transplants.

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*Nicolas Papon, Gilles Nevez, Solène Le Gal, Cécile Vigneau, Florence Robert-Gangneux, Jean-Philippe Bouchara, Oliver A Cornely, David W Denning, *Jean-Pierre Gangneux*
jean-pierre.gangneux@chu-rennes.fr

Host-Pathogen Interaction Study Group, GEIHP, EA 3142, SFR ICAT 4208, University of Angers and University of Western Brittany, Angers, France (NP, J-PB); Host-Pathogen Interaction Study Group, GEIHP, EA 3142, SFR ICAT 4208, University of Angers and University of Western Brittany, Brest, France (GN, SLG); Parasitology-Mycology Unit, Brest University Hospital, Brest, France (GN, SLG); University of Rennes, CHU Rennes, ISNERM, EHESP, IRSET, UMR_S 1085, F-35000 Rennes, France (CV, FR-G, J-PG); Division of Nephrology, Rennes University Hospital, Rennes, France (CV); Parasitology-Mycology Unit, Rennes University Hospital, Rennes, France (FR-G, J-PG); Parasitology-Mycology Unit, Angers University Hospital, Angers, France (J-PB); Excellence Center for Medical Mycology, Department I of Internal Medicine, Medical Faculty and University Hospital Cologne, and Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, German Centre for Infection Research (DZIF), Partner Site Bonn-Cologne, University of Cologne, Cologne, Germany (OAC); Global Action Fund for Fungal Infections, Geneva, Switzerland (DWD); Manchester Academic Health Science Centre, University of Manchester, Manchester, UK (DWD)

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