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Infections in the solid-organ transplant recipients

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Abstract. *The advancement in the field of transplant has led to the increasing number of solid-organ transplant recipients (SOTRs). This success leads to novel confronts in communicable infections, which are compound by the emergence of newly contagious and antimicrobial drugs resistant microorganisms. The prevention of infections is a cornerstone of any modern solid organ transplantation program. Understanding the fundamentals of these infections with early detection is crucial for improving the outcomes of such patients and lowers the probable extra complications. The probability of critical infections in SOTRs is established by relations between the patient's epidemiological exposures and the net condition of immune repression. A timeline was formed to build up a discrepancy diagnosis of infection in SORTs. The improvement in screening, the investigations including imaging and molecular techniques and prophylactic intervention protocols, has made it promising to limit the penalty of infections and act towards better patient endurance. Pre-transplant screening of the prospective organ donor and recipient provides a chance to evaluate the viability and wellbeing of transplantation, to decide the prophylaxis and protective approaches developed post-transplant, to find out and entirely treat active infection in the possible recipient proceeding to transplant, to renovate the vaccination condition of the potential recipient.*

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Інфекції у реципієнтів трансплантату солідного органу

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Резюме. *Прогрес у галузі трансплантації привів до збільшення кількості реципієнтів трансплантату солідного органу (РТСО) та нових протистоянь з інфекційним ускладненнями, появою нещодавно контагіозних та стійких до антибактеріальних лікарських засобів мікроорганізмів. Профілактика інфекцій є наріжним каменем будь-якої сучасної програми трансплантації. Розуміння основ цих інфекцій з ранньою діагностикою має вирішальне значення для поліпшення результатів лікування РТСО. Імовірність критичних інфекцій у РТСО визначається залежно від епідеміологічного стану та імунної реакції реципієнта. Покращення скринінгу, обстеження, включаючи візуалізацію і молекулярні методи дослідження та протоколи профілактичного втручання, продемонструвало перспективу зменшення інфекційних ускладнень та підвищення виживаності трансплантату. Передтрансплантаційний скринінг потенційного донора та реципієнта надає можливість прогностичної оцінки трансплантації, визначити посттрансплантаційні профілактичні та лікувальні підходи, вчасно діагностувати та вилікувати активну інфекцію та оновити стан вакцинації у потенційного реципієнта.*

Ключові слова: *реципієнт, солідний орган, трансплантація, інфекції, фактори ризику, хронологія, профілактика.*

Introduction. Solid-organ transplantation (SOT) is a life-saving practice for patients with end-organ diseases [1]. The former transplant was performed in 1954; then transplants have become progressively widespread with an exceptional patient and graft outcomes [2]. Globally, the organ transplantation number has augmented from 19,864 in the year 2000 to 139,024 in 2017 and kidney and liver transplantation accounts for about 88% of total transplantations [3]. The durability of the transplanted kidney with the 10-year graft survival is 82% [4] and the 5-year survival rate in liver transplantation is 81.2% of patients [5].

Medical improvement in screening, diagnosis, surgical procedures, immunosuppressive drugs, and antimicrobial prophylaxis has resulted in significantly reduced morbidity and mortality after organ transplantation [6]. However, because solid organ transplant recipients (SOTRs) have a continuously increasing life expectancy, they are also exposed to immunosuppressants for a longer time, making the SOTRs more susceptible to infections [7]. These infections are mainly owing to the reception of marginal donors, surgical intervention and immunosuppressive drugs [8].

A broad range of potential microorganisms infects immunosuppressed persons. Physical signs of infection and fever are reduced; infection may be signaled by more precise laboratory or radiographic abnormalities. Major infections such as peritonitis may be deficient in fever or localized signs. Fever can be absent in about 40% of infections, particularly in infections caused by fungi [9].

The challenges for prevention, diagnosis and management of infectious diseases include the lack of assays to evaluate hazards for certain infections or graft rejection, suboptimal screening standards for microbiologic assessment of organ donors, rising resistance to antimicrobial agents, viruses that cause cancer and alters the worldwide configuration of infections. Continuous evaluation of the epidemiology of those infections and assessment of the modalities of prevention and therapy are vital for further enhancement of outcomes in SOTRs [9].

The aim of this state of the art is to focus on the latest advances in the prevention of infections in SOTRs that may take place at various phases of the transplant procedure. The appearance of some recent donor-derived infections will be illustrated, and then a summary of novel agents accessible for prophylaxis of infections in SOTRs and lastly the possible role for the newer vaccines will be discussed.

Risk factors of SOT infections. The risk of infection for the recipient at any point in time after transplantation is predisposed by a multitude of factors, including the epidemiologic exposures and the net state of immunosuppression [2].

Epidemiologic Exposures. The microorganisms in tissues and on barrier surfaces are termed the "microbiome" including both commensal flora and acute exposures (infection). The microbiome of the transplant recipient is derived from multiple sources: prior colonization of mucosal surfaces, latent infections, infection from the organ donor and new community-derived or nosocomial exposures [2].

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The microbial networks are disrupted in transplant recipients by immunosuppression, infectious exposures, antimicrobial therapies, metabolic disorders and surgery. Changes in microbial diversity (types, distribution, and concentrations of organisms) and new exposures alter local and systemic immunity and may affect graft outcomes [10].

Donor- and recipient-derived infections. Donor-derived infections can be defined as any infection present in the donor that is transmitted to one or more recipients [6, 11]. A variety of pathogens can be transmitted by the transplanted organ (Table 1) [12]. These infections are suspected when clusters of infections sharing unusual clinical symptoms occur among recipients sharing a common donor, or when a recipient develops a disease for which he had no exposure [10].

Table 1

Pathogens Reported to be transmitted with Solid Organ Transplantation [12].

Bacteria	**Mycobacteria**
Staphylococcus aureus	*Mycobacterium tuberculosis*
Klebsiella species	Non-tuberculous mycobacteria
Bacteroides fragilis	**Parasites/Protozoa**
Pseudomonas aeruginosa	*Toxoplasma gondii*
Escherichia coli	*Strongyloides stercoralis*
Salmonella species	*Plasmodium species*
Yersinia enterocolitica	*Trypanosoma cruzi*
Treponema pallidum	*Pneumocystis jirovecii*
Brucella species	**Viruses**
Enterobacter species	Cytomegalovirus (CMV)
Acinetobacter species	Epstein-Barr virus (EBV)
Legionella species	Herpes simplex virus(HSV)
Nocardia species	Varicella-zoster virus (VZV)
Listeria monocytogenes	Human herpesvirus-6,7 and 8 (HHV)
Fungi	Hepatitis B and D virus (HBV, HDV)
Aspergillus species	Hepatitis C virus (HCV)
Candida species	Human immunodeficiency virus (HIV)
Coccidioides immitis	Parvovirus B19
Cryptococcus neoformans	Rabies
Histoplasma capsulatum	Lymphocytic choriomeningitis virus
Scedosporium apiospermum	West Nile virus (WNV)
Prototheca species	BK virus
Zygomycetes	Human T-cell lymphotropic virus-1/2 (HTLV 1/2)

Donor-derived infections can be categorized into two groups: "expected" and "unexpected" infections. Expected transmissions occur when the donor is known to have an infection, as demonstrated by positive serology or nucleic acid test or positive cultures, in the donor at the time of donation [13]. Unexpected transmissions occur when a donor is not known to be infected prior to donation, but one or more transplant recipients develop an infection derived from the common donor [14]. Such transmissions occur when either clinical disease in the donor was not recognized at the time of donor death, or screening was not performed for the pathogen of interest [15].

Community exposures. Travel, hobbies, young children and work environments provide exposures to contaminated food and water (*Listeria monocytogenes*) [16], soil (Aspergillus or Nocardia species) [17, 18], birds (*Cryptococcus neoformans*) [19] and geographically restricted mycoses (*Blastomyces dermatitidis, Coccidioides immitis, Paracoccidioides species and Histoplasma capsulatum*) [20] in addition to outbreaks of respiratory viruses and arthropod-borne diseases [16].

Nosocomial exposures. Colonization with antimicrobial-resistant organisms may result from prolonged hospitalizations of organ donors and transplant recipients. The mortality associated with multi-drug resistant

organisms (MDRO) infections in transplant recipients is increased. MDRO include carbapenem-resistant enteric Gram-negative bacteria, often Klebsiella species [21]. Common post-surgical infections include vancomycin-resistant enterococci, methicillin-resistant staphylococci [22], Clostridium difficile colitis [23] and fluconazole-resistant Candida species [24, 25]. Respiratory viral infections may be acquired from medical staff [16].

Net state of immunosuppression. The net state of immunosuppression is a conceptual measure of all factors contributing to the patient's risk of infection (Table 2) [9]. An estimation of the net state of immunosuppression provides a way of risk stratifying for the development of opportunistic infections. No single assay or score that adequately defines the net state of immunosuppression has been developed or validated [2].

Table 2

Factors contributing to the net state of immunosuppression [9]

• Immunosuppressive Therapy: Type and Intensity.
• Prior therapies (Chemotherapy or Antimicrobials).
• Mucocutaneous Barrier Integrity (catheters, lines and drains).
• Neutropenia, Lymphopenia and Hypogammaglobulinemia (often drug-induced).
• Technical complications (graft injury, fluid collections and wounds).
• Underlying immune defects (autoimmune disease).
• Metabolic conditions: uremia, malnutrition, diabetes, alcoholism/cirrhosis and advanced age.
• Viral infection (e.g., herpesviruses, hepatitis B and C, HIV, RSV and influenza).

HIV: human immunodeficiency virus; RSV: respiratory syncytial virus.

Timeline of sot infections. Classically, infections occur in 3-time phases [9]. This timeline is used to (1) establish a differential diagnosis for the SOTRs suspected of having the infection, (2) identify excess environmental hazards or over-immunosuppression and (3) design preventative antimicrobial strategies [26]. Infections occurring at the "wrong" time suggest an excessive epidemiologic hazard or excessive immunosuppression [2].

Phase I: one-month post-transplantation. During the first month after transplantation, infections result from surgical complications, donor-derived infections, preexisting recipient infections and nosocomial infections including aspiration or *Clostridium difficile* colitis [23]. Early infections often reflect technical issues (bleeding, strictures, leaks, and graft injury) [24] or hospital environmental exposures e.g. Aspergillus pneumonia with hospital construction [17].

Phase II: 1 to 12 months post-transplant. The differential diagnosis of infections in this period includes the remaining infection from the presurgical period including Clostridium difficile colitis and residual pneumonia [23, 24]. It also, involves viral infections such as CMV [27], HSV [28], VZV [29], EBV [30], HHV 6 or 7 [31], BK polyomavirus [6], relapsed hepatitis (HBV and HCV) [32] and the community-acquired respiratory viruses (adenovirus, influenza, parainfluenza, respiratory syncytial virus and metapneumovirus) [33]. In addition, opportunistic infection due to Pneumocystis jiroveci [34], Listeria monocytogenes [16], Toxoplasma gondii [35], Nocardia species [18], Aspergillus species [17] and endemic fungi [20] are implicated as well.

Phase III: more than 6–12 months post-transplant. SOTRs suffer from community-based epidemiological exposures including gardening, community cleaning activities, exposure to construction, travel to the developing world and contact with individuals with active transmissible infections. Major challenges include late CMV, EBV, JC polyomavirus and HPV infections. SOTRs with high levels of maintenance suppression has risk to have common opportunistic pathogens (e.g. Pneumocystis jirovecii, Listeria monocytogenes, nocardia and aspergillus species or Cryptococcus neoformans), molds and common diseases (VZV and HSV) of unusual severity [9].

Prevention of sot infections.

Donor and Recipient Microbiologic Screening. There are a number of ways to mitigate the risk of donor-derived infections. These can be classified as: risk stratification from the donor's medical and social history, careful clinical assessment of the donor and the donor organs and laboratory screening of the donor for infections [6, 11, 36]. Donor and recipient microbiologic screening provides essential data for the development of post-transplant preventative strategies (Table 3) [12].

Table 3

Infectious diseases screening for recipients and donors prior to transplantation [12]

Test	Recipient	Deceased donor	Living donor
Viral			
Human Immunodeficiency Virus (HIV)			
HIV antibody/antigen (fourth Generation HIV screening test)	√	√	√
HIV NAT		√	√
Cytomegalovirus (CMV)			
CMV IgG antibody	√	√	√
Hepatitis B virus (HBV)			
HBV surface antigen (HBsAg)	√	√	√
HBV core antibody (HBcAb-IgM and IgG, or total core antibody)	√	√	√
HBV surface antibody (HBsAb)	√		
HBV NAT		√	√
Hepatitis C virus (HCV)			
HCV antibody	√	√	√
HCV NAT	√	√	√
Epstein-Barr virus (EBV)			
EBV Viral capsid antigen IgG and IgM antibodies	√	√	√
West Nile virus (WNV)			
WNV serology or NAT (seasonal).			√
Parasitic			
Toxoplasma gondii			
Toxoplasma IgG antibody.	√	√	√
Strongyloides stercoralis			
IgG antibody (endemic areas).	√	√	√
Trypanosma cruzi			
Serology (if from endemic areas).	√	√	√
Fungal			
Coccidioides immitis			
Serology (if from endemic areas).	√	√	√
Bacterial			
Treponema pallidum (T. pallidum) (any of the following)	√	√	√
Fluorescent treponema antibody absorption			
T. pallidum particle agglutination.			
T. pallidum enzyme immunoassay.			
Rapid plasma reagin.			
Venereal Disease Research Laboratory.			
Mycobacterium tuberculosis (any of the following)	√		√
Purified protein derivative.			
Interferon gamma release assay.			
Urine culture		√	
Blood culture		√	

Following viral infection, there is a period of time in which the virus is either transiently in the blood or at levels below the limit of detection of the most nucleic acid test (NAT); this is termed the NAT window or eclipse period (Table 4) [6].

Table 4

The estimated "window period" in microbiologic screening of potential organ donors [6]

Virus	Serology	NAT
HIV	22 days	5.6-10.2 days
HBV	38.3-49.7 days	20.4-25.7 days
HCV	38-94 days	6.1- 8.7 days

During this period, there may be a replication of the virus in target tissue that may get transplanted into a recipient from the donor despite negative NAT results. Even though eclipse window periods exist and therefore NAT is less helpful for very recent donor virus acquisitions. Consequently, NAT can still pick up recent infections more readily than serology alone [37]. After a period of ongoing viral replication, the patient eventually develops detectable antibodies documenting exposure to the virus. The period between infection and initial detection of virus-specific antibodies is termed the serologic window. Several donor-derived infections have been transmitted during this serologic window [38].

Donor microbiologic screening.

Bacterial infections. Bacterial infections should have appropriate treatment prior to donation. If a deceased donor is determined to have an active bacterial infection based on cultures, antibiotics should be administered to the recipient for at least 14 days for infections with Gram negative bacilli or *Staphylococcus aureus*. A shorter course of therapy may be considered for less virulent organisms [12]. SOTRs from a deceased donor with non-bacteremic, localized infection not involving the transplanted organ do not require treatment, with the exception of meningitis, in which occult bacteremia frequently occurs. For potential lung donors, bronchoscopy with cultures should be performed and appropriate antibiotics initiated in the recipient to cover recovered bacteria [39]. *Treponema pallidum* has rarely been transmitted by transplantation, but it is not a contraindication to deceased organ donation if the recipient is treated post-transplant with an appropriate course of penicillin [12]. Donors in whom active *Mycobacterium tuberculosis* (TB) is clinically possible should not be used [40]. Living donors should have purified protein derivative (PPD) testing performed or interferon-gamma release assays (IGRA) testing; if either test is positive, a chest radiograph should be obtained to look for evidence of active pulmonary infection [41]. Deceased donors with a history of an untreated latent TB infection (LTBI) and without evidence of active disease are acceptable but warrant consideration of the treatment of the recipient with isoniazid [42].

Fungal infections. Routine donor screening of all donors for *Histoplasma capsulatum* from an endemic area is not warranted. However, explanted organs that may have granuloma should prompt fungal culture and testing for antigen and antibodies to Histoplasma capsulatum [12]. Screening for *Coccidioides immitis* should be considered in living donors from endemic areas. Universal screening is not recommended for those outside the endemic area [20]. Screening of *Cryptococcus neoformans* should be considered in donors who have meningoencephalitis, pulmonary nodules, or fever of unknown etiology if they have underlying medical conditions that predispose to this infection [19].

Parasitic infections. *Toxoplasma gondii* screening by serology is mandatory in all donors. Donor seropositivity for Toxoplasma gondii is not a contraindication to organ donation but appropriate prophylaxis should be administered to the recipient [43]. Screening for endemic infection including *Trypanosoma cruzi* and *Strongyloides stercoralis* should be performed based on epidemiologic risk factors. Transplantation of the hearts from donors with positive *Trypanosoma cruzi* serology should be avoided [6, 44].

Viral infections. All donors should be screened for CMV, EBV, HBV, HCV, and HIV [32, 45]. NAT is used in addition to serology for HCV screening of deceased donors [46]. HBV, HCV, and HIV screening of living donors should be close as possible to but no longer than 28 days prior to organ procurement [12]. Due to the low seroprevalence of HTLV-1 in the United States and the poor positive predictive value of screening HTLV-1/2 assays in this population, routine screening of all deceased donors is not recommended [12]. Living donors should have WNV NAT close to the time of transplant. Donors with any form of unexplained or confirmed WNV encephalitis should be avoided [47, 48]. More recently, screening of the Zika virus should emphasize on recent travel history and epidemiologic risk factors, as well as recent donor symptoms [6]. Routine screening is not currently recommended and if screening is to be used in selected donors, blood NAT is preferred [49, 50].

Recipient microbiologic screening.

Pre-transplant detection of active bacterial infection. In general, active or uncontrolled infection in the potential recipient should delay transplant until the infection resolves or is controlled [12]. All SOTRs should have a PPD or IGRA performed prior to transplant, and those who have a positive skin test or IGRA, or a history of active tuberculosis, should undergo additional screening to rule out active disease. SOTRs with LTBI should be given prophylaxis to prevent the reactivation of disease [42].

Fungal infections. A pre-transplant recipient with invasive fungal infection should be treated at least until there is radiographic, clinical and microbiologic resolu-

tion in order to minimize the risk of this high-mortality infection post-transplant [12]. Pre-transplant screening for endemic mycoses is most useful in areas endemic for *Coccidioides immitis*, where a pre-transplant history of active disease and/or seropositivity may prompt lifelong azole prophylaxis. Pre-transplant screening for *Histoplasma capsulatum* is not recommended [20].

Parasitic infections. SOTRs with known endemic exposure to *Strongyloides stercoralis* and *Trypanosoma cruzi* should be screened. Serologic screening for *Strongyloides stercoralis* is preferred over stool examinations [44]. *Toxoplasma gondii* serology should be performed in all patients undergoing organ transplantation; in particular heart transplant recipients; seronegative recipients with seropositive donors and seropositive recipients should receive prophylaxis [6, 35].

Viral infections. Screening for CMV, EBV, HBV, HCV, and HIV should be performed in all transplant recipients. Active viral infection in potential SOTRs should be delayed if possible until the infection resolves. VZV and MMR screening of SOTRs is important, with vaccination of the seronegative recipient pre-transplant if possible [12].

Antimicrobials prophylaxis for SOTRs infections

Antibacterial prophylaxis. Perioperative antibacterial prophylaxis to prevent wound infections begins in the operating room and continues for <24 hours and <3 days after transplantation, in kidney transplant and other SOTRs, respectively [24]. Trimethoprim/sulfamethoxazole prophylaxis for the first 6 months after transplantation is recommended to protect against urinary tract infections. This regimen also protects against infection with *Pneumocystis jirovecii, Listeria monocytogenes, Nocardia* species and *Toxoplasma gondii* [16, 18, 35, 39]. SOTRs with positive PPD test results and a high risk of tuberculosis reactivation should be given 9-12 months of isoniazid therapy after transplantation. Isoniazid prophylaxis should be considered for SOTRs from donors with a history of tuberculosis or tuberculin reactivity [42].

Antibacterial regimens should be individualized by the type of organ transplant. Kidney transplant patients are given cefazolin or ampicillin-sulbactam, to cover uropathogens and staphylococci. Gram-negative coverage is added for pancreas transplant recipients. Extended-spectrum cephalosporins are given to liver transplant recipients to cover gram-negative bacilli, enterococci and staphylococci [21]. Recently, the combination of new beta-lactam drug ceftolozane with tazobactam has a broad-spectrum activity against *Enterobacteriacae* producing extended-spectrum beta-lactamase. Ceftolozane-tazobactam is used for the treatment of multidrug-resistant *Pseudomonas* infections and complicated intra-abdominal and urinary tract infections [51]. Another interesting antibacterial agent is the association of ceftazidime with a new beta-lactamase inhibitor, avibactam, which inhibits the activity of some carbapenemases [21, 52]. Besides the use of antibiotics active against *Clostridium difficile*, (vancomycin, metronidazole, and fidaxomicin), other approaches are in development. Fecal transplantation appears beneficial for preventing relapses in immunocompetent hosts. However, the use in SOTRs has been limited because of concerns about side effects. More recently, two monoclonal antibodies directed against *Clostridium difficile* toxin A and toxin B-actoxumab and bezlotoxumab, respectively have been developed and their potential benefit in SOTRs needs to be determined [23].

Fungal infections. All transplant recipients in endemic areas for *Coccidioides immitis* should receive azole prophylaxis for 6-12 months after transplant. Recipients of organs from donors with prior or active infection should receive azole prophylaxis. Primary antifungal prophylaxis for *Histoplasma capsulatum* and *Cryptococcus neoformans* after transplant is not recommended [19, 20]. For *Candida* infection, targeted prophylaxis in SOTs with azoles or echinocandins is preferred over lipid formulations of amphotericin B [25]. Anidulafungin, micafungin or caspofungin in standard dose or azoles (voriconazole, itraconazole or posaconazole) is recommended for the use of prophylaxis against invasive aspergillosis in SOTRs. Inhaled amphotericin B or lipid preparation of amphotericin B can be used for prophylaxis postoperatively in patients with lung transplants [17]. Isavuconazole, a new triazole agent with broad activity, has been approved for fungal infections including Aspergillus and Mucor species. Isavuconazole has less liver toxicity than voriconazole, and a lack of nephrotoxicity, which can be an issue with liposomal amphotericin B. The role of isavuconazole in the prophylaxis and treatment of fungal infections in SOTRs needs to be determined [20].

Viral infections. The antiviral drugs for CMV prophylaxis are valganciclovir and intravenous ganciclovir. For kidney recipients, a high dose of valacyclovir is used. CMV prophylaxis has the advantage of preventing HSV, VZV, HHV6, and HHV7 infections. Alternative drugs such as foscarnet and cidofovir carry significant toxicities [28, 29, 31]. Letermovir, a novel viral terminase inhibitor, was recently approved for CMV prophylaxis after bone marrow transplantation. A successful outcome was reported with the use of letermovir in a lung transplant patient with CMV-resistant disease and was effective in treating CMV viremia in kidney transplant recipients. However, the occurrence of resistance has been reported in treatment with letermovir alone [53]. The new antiviral drug, maribavir is an inhibitor of the viral kinase. Its efficacy for the treatment of refractory or resistant CMV disease in SOTRs has been reported with higher doses. Occurrence of resistance has been reported in treatment with maribavir. Another new antiviral drug, Brincidofovir, the lipid-conjugated analog of cidofovir, has high oral availability and less nephrotoxicity than cidofovir. Efficacy has been low in prevention in hematopoietic stem cell transplant patients, and few data are available in SOT recipients [53].

Vaccination of SOTRs. Vaccination status should be reviewed and a vaccination plan developed in all SOTRs (Table 5) [54].

Table 5

Recommendations for Immunization of Adult SOTRs [54]

Vaccine	Inactivated /live Attenuated (I/LA)	Recommended Before transplant	Recommended after transplant	Evaluate for serologic response
Influenza	I	Yes	Yes	No
	LA	*	No	No
Hepatitis B	I	Yes	Yes	Yes
Hepatitis A	I	Yes	Yes	Yes
Tetanus	I	Yes	Yes	No
Pertussis (Tdap)	I	Yes	Yes	No
Inactivated Polio vaccine	I	Yes	Yes	No
H influenza type B	I	Yes	Yes	Yes
Streptococcus pneumonia (conjugate vaccine)	I	Yes	Yes	No
Streptococcus pneumonia (polysaccharide vaccine)	I	Yes	Yes	No
Rabies	I	Yes	Yes	Yes
Human papilloma virus	I	Yes	Yes	No
Varicella (live attenuated; Varivax)	LA	Yes	No	Yes
Varicella (live attenuated; Zostavax)	LA	Yes	No	No
Varicella (subunit; Shingrix)	I	Yes	Yes	No
MMR(Measles/Mumps/Rubella)	LA	Yes	No	Yes
BCG	LA	Yes	No	No
Smallpox	LA	No	No	No
Anthrax	I	No	No	No

* If a live-attenuated influenza vaccine was to be administered accidentally to SOTRs, antiviral therapy and subsequent revaccination with an inactivated influenza vaccine can be considered.

Inactivated vaccines should be given at least 2 weeks prior to transplant where possible for an adequate immune response. Live-attenuated vaccines should be given at least 4 weeks prior to transplant to ensure that vaccine-related viral replication has resolved prior to transplant [55]. In the post-transplant setting, inactivated vaccines can be administered starting at 3-6 months post-transplant. For transplant recipients who intend to travel to areas of increased risk for infection, travel-specific vaccinations should be addressed (Table 6) [54].

Table 6

Travel vaccine recommendations for SOTRs [54]

Vaccine	Inactivated /live attenuated (I/LA)	Can be administered before the transplant	Can be administered after transplant	Evaluate for serologic response
Yellow fever a	LA	Yes	No	No
Japanese encephalitis	I	Yes	Yes	No
Salmonella typhi (Typhim Vi, intramuscular)	I	Yes	Yes	No
Salmonella typhi (Vivotif, oral)	LA	Yes	No	No
Traveler's diarrhea and cholera vaccine (Dukoral) b	I	Yes	Yes	No
Cholera Vaccine (Vaxchora)	LA	Yes	No	No

[a] Yellow fever vaccination may be required for travel to some countries of Africa and South America but should be waived if travelers are immunosuppressed.

[b] Oral inactivated vaccine against Cholera and Enterotoxigenic *Escherichia coli* provides short-term protection.

Influenza vaccine can be given as early as 1-month post-transplant and high-dose or booster dosing of Influenza vaccine has greater immunogenicity and is preferred over a single standard dose [56]. Hepatitis B vaccine accelerated schedules such as 0, 1, 2 months or 0,7,21 days can be used. A higher dose (40μg) vaccine can be used in end-stage renal disease and post-transplant settings. Titers can be monitored for vaccine response and revaccination performed if necessary [57]. There are two main formulations of pneumococcal vaccine: a 23-valent polysaccharide vaccine (PPSV23) and a 13-valent protein-conjugated vaccine (PCV13). Both PCV13 and PPSV23 pneumococcal vaccines should be administered to SOTRs. In vaccine naïve patients, PCV13 can be administered first followed by PPSV23, a minimum of 8 weeks later. A PPSV23 booster can be given after 5 years [54]. HPV vaccination can be administered before or after transplantation to at-risk patients meeting specific age criteria. MMR and live attenuated varicella vaccination is generally contraindicated post-transplant [54].

The Egyptian Experience in SOT. In Egypt, the first renal transplant was performed at Al-Mansoura University Hospital in 1976. Following a very slow start, the number of transplants gradually increased, reaching an annual rate of 90-100 transplants. Presently, there are 80 centers that perform renal transplantation in Egypt, with the overall experience exceeding 7000 living donors [58].

Many Egyptian studies reported various infections among kidney transplant recipients (KTRs). In a recent study by *El Maghrabi et al.* [59] in Mansoura Urology and Nephrology Center, 394 KTRs out of 2700 (14.6%) were shown to be HCV antibody positive. Among the 394 patients, 114 (28.9%) were positive for HCV RNA. In other reports from Mansoura Urology and Nephrology Center, *Alsaid et al.* [60] declared the occurrence of H1N1 influenza virus infection in 25 (48.1%) out of 52 clinically suspected KTRs, while *El-Agroudy et al.* [61] stated that, of 1200 KTRs, 45 (3.8%) patients developed post-transplant Tuberculosis. Also, *Bakr et al.* [62] observed skin infections in 191(63.25%) of KTRs including folliculitis (10.3%), tinea versicolor (30.1%), dermatophytosis (19.5%) and onychomycosis (7.6%) The experience Cairo University hospitals in kidney transplantation were elaborated by a retrospective study conducted on 282 patients by *Saadi et al.* [58]. The researchers found that infections among the KTRs were detected in 18.8%, of whom 32.1% were infected with cytomegalovirus and 67.9% were infected with other bacterial and fungal infections.

Regarding living donor liver transplant (LDLT), it was first performed in Egypt in 1991 at the National Liver Institute, Menoufeya University. By that time, there was an increase in the number of LDLT centers (13 centers) and cases (2,500) with the improvement of the results of LDLT [63]. Egypt has the highest incidence of HCV in the world. The incidence of HCV antibodies and HCV RNA in individuals from 15 to 59 years old were 14.7% and 9.8%, respectively, in 2008 [59].

The high prevalence of chronic liver diseases has led to increasing numbers of Egyptian patients suffering from end-stage liver disease (ESLD), necessitating liver transplantation [64]. *Yosry et al.* [65] showed that hepatitis C-related ESLD is the main indication for liver transplantation and represents 89.8% of cases in Egypt, while HBV and other indications represent 5.1% and 5.1% respectively. The exact recipient survival among the Egyptian liver transplant recipients is not accurately known however, *Amer and Marwan* [66] documented that, the one-year, three-year and five-year survival were 73.17%, 70.83% and 64.16% respectively in the International Medical Center, Cairo in a series of 145 adult to adult LDLT cases and there was no donor mortality.

Several Egyptian pieces of the research reported the occurrence of post-transplant infections in LDLT patients. In a recent study by *Saleh et al.* [64], post-transplant-infections occurred in 8 (16%) out of 50 LDLT patients. Intra-abdominal infections were the most frequently encountered infection, of which *Enterococcus* species were the leading pathogens. *Montasser et al.* [67] in the prospective study included 45 patients who underwent LDLT at Ain Shams Center for Organ Transplant, 33 patients (73.3%) were suffered from bacterial infections. The study done in National liver institute Menoufya in 2015 showed that the HCV recurrence was 19.2% [68]. Thus, the previous studies declared that SOT is successfully done in Egypt with similar results worldwide.

Conclusion. The advancement in the field of transplant has led to the increasing number of SOTRs, with better survival rates. This success leads to new challenges in infectious diseases, which are compound by the emergence of newly transmissible and multidrug-resistant organisms. The prevention of infections is a cornerstone of any modern solid organ transplantation program. Understanding the fundamentals of these infections with early detection is critical for improving the outcomes of such patients and reduces the potential for further complications.

The risk of serious infections in SOTRs is determined by interactions between the patient's epidemiological exposures and net state of immune suppression. A timeline was created to develop a differential diagnosis of infection in transplantation based on common patterns of infectious exposures, immunosuppressive management and antimicrobial prophylaxis. Thus, improvement in conceptions of the immunosuppression, the risks of rejection and infection, the advances in screening, the diagnostic tests including imaging and molecular techniques and prophylactic intervention protocols, have made it possible to manage and restrict the consequences of infections and work towards better patient survival among SOTRs.

Furthermore, pre-transplant screening of the potential organ donor and recipient affords an opportunity to assess the feasibility and safety of transplantation, to determine the prophylaxis and preventive strategies utilized post-transplant, to detect and fully treat active infection in the potential recipient prior to transplant, to update the vaccination status of the potential recipient, and to sufficiently educate the patient and family about preventive measures.

Future prospective. Future advances will incorporate the use of rapid molecular diagnostic testing and possibly additional testing for emerging pathogens in clinical practice. There is a need for the development of quantitative tests which can identify the nucleic acids or microbial antigens with an enhancement of the diagnostic accuracy. Such tests would help the physician to guide and individualize antimicrobial prophylaxis and therapy, thereby reducing the toxicity of these agents.

The development of newer antimicrobials possessing a better toxicity profile will shape the future of organ transplantation. In the very near future, the progress in treating infectious diseases (for instance, hepatitis C) can have a significant impact on organ donation. New researches in the development of novel highly potent antivirals for both HIV and HCV may result in single pill treatment options allowing for simplification and improved tolerability. Future researches in nanomedicine showed that the delivery of ultra-low-dose medication to the graft tissues and nanoimaging can enable graft surveillance through non-invasive immunomonitoring of donor and recipient cells. Together, therapies can be personalized with minimizing adverse effects as seen with systemic treatments. Beyond improvement in outcomes, the economic justification and savings in healthcare costs through nanomedicine strategies could be significant.

Vaccination of SOTRs remains a critical component of preventing infection related morbidity and mortality. Additional research is needed in SOTRs to evaluate the efficacy and the optimization of vaccine responses including evaluation of time from transplant, immunosuppressive interactions, and vaccination formulations and dosing. As SOTRs may have decreased immunogenicity to vaccination, the inclusion of SOTRs in research studies with novel vaccines is essential to ensure this at-risk population can be protected.

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