

South Asian Transplant Infectious Disease Guidelines for Solid Organ Transplant Candidates, Recipients, and Donors

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Abstract. These guidelines discuss the epidemiology, screening, diagnosis, posttransplant prophylaxis, monitoring, and management of endemic infections in solid organ transplant (SOT) candidates, recipients, and donors in South Asia. The guidelines also provide recommendations for SOT recipients traveling to this region. These guidelines are based on literature review and expert opinion by transplant physicians, surgeons, and infectious diseases specialists, mostly from South Asian countries (India, Pakistan, Bangladesh, Nepal, and Sri Lanka) as well as transplant experts from other countries. These guidelines cover relevant endemic bacterial infections (tuberculosis, leptospirosis, melioidosis, typhoid, scrub typhus), viral infections (hepatitis A, B, C, D, and E; rabies; and the arboviruses including dengue, chikungunya, Zika, Japanese encephalitis), endemic fungal infections (mucormycosis, histoplasmosis, talaromycosis, sporotrichosis), and endemic parasitic infections (malaria, leishmaniasis, toxoplasmosis, cryptosporidiosis, strongyloidiasis, and filariasis) as well as travelers' diarrhea and vaccination for SOT candidates and recipients including travelers visiting this region. These guidelines are intended to be an overview of each topic; more detailed reviews are being published as a special supplement in the *Indian Journal of Transplantation*.

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INTRODUCTION

Infections are an important cause of morbidity and mortality in solid organ transplant (SOT) recipients.¹ Although many infections are common worldwide, there are differences in rates and types of infections in various geographic locations. According to Transplant data from Global

Observatory on Donation and Transplantation, an estimated 13700 SOTs were performed in South Asia (SA) (India, Pakistan, Bangladesh, Nepal, Sri Lanka, Bhutan, Maldives) in 2019, of which 12666 (92%) were done in India² (Figure 1). A majority (10635) were kidney transplants, followed by liver (2708), heart (218), lung (114),

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FIGURE 1. Map of South Asian region with number of solid organ transplants (2019). Total number of solid organ transplants in South Asia, $n = 13\,700$.²

and pancreas (25).² About 83% of kidney and 66% of liver transplants used living donors, which puts India among the countries with the highest numbers of living donors for SOTs (Table 1). In addition to performing transplants for its own citizens, Indian centers perform transplant procedures for patients from the Middle East, Africa, Myanmar, Afghanistan, Nepal, and central Asia (Uzbekistan, Tajikistan, Turkmenistan, Kirgizstan).

The SA region is home to many tropical diseases and accounts for one-quarter of the world's soil-transmitted helminth infections, one-third of the global deaths from rabies, and 50% of the global burden of lymphatic filariasis, visceral leishmaniasis (VL), and leprosy.³ The region is also experiencing an emerging problem with major arbovirus infections, that is, Dengue, Japanese encephalitis, Chikungunya, and Zika Virus. Other important neglected tropical diseases, such as strongyloidiasis, toxocarasis, leptospirosis, and amebiasis, also represent a significant burden.³

Travel to and from this region for tourism and work is common, including for transplant recipients. According to data from the Indian Ministry of Tourism, approximately 18 million international tourists visited India in

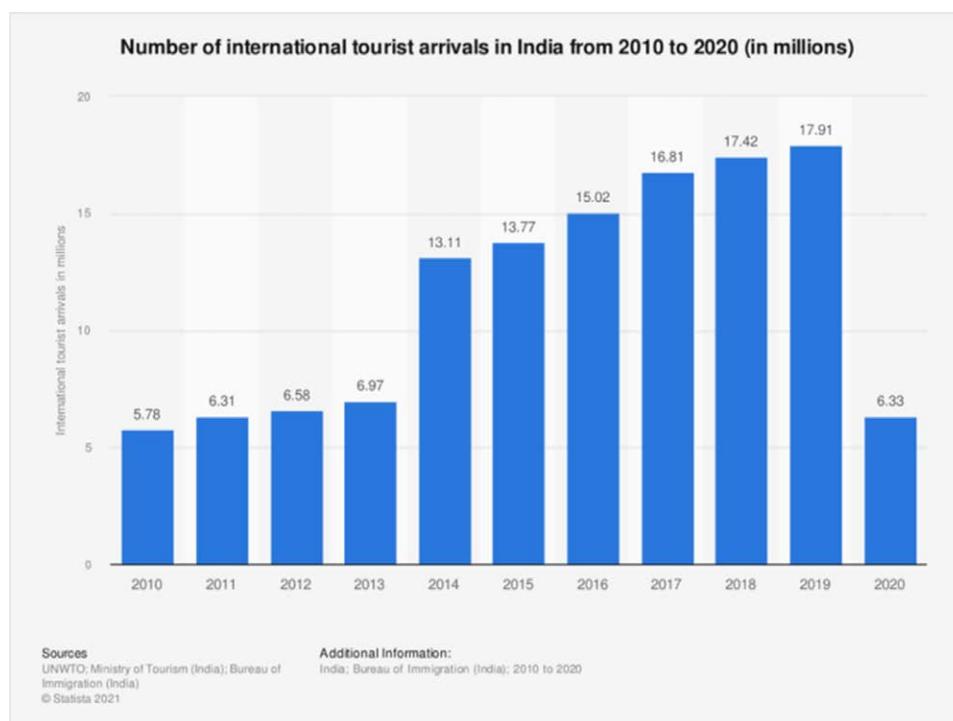
2019 (Figure 2). Other infection risks for travelers include malaria, dengue, chikungunya, typhoid, hepatitis, and tuberculosis (TB).⁴

Thus far, there are no guidelines for screening SOT recipients (SOTRs) and donors for these endemic infections in SA, the best methods of prevention and prophylaxis, and what advice should be given to recipients traveling in and out of this region. Similar guidelines have been developed for other geographic regions.⁵⁻⁸ To address this unmet need, a SA transplant working group including transplant physicians, transplant surgeons, and infectious disease specialists from India, Pakistan, Sri Lanka, Bangladesh, Nepal, and other parts of the world was created. The first meeting of the working group was done in February 2019, and it was attended by leading transplant physicians, surgeons, and infectious disease specialists from various reputed institutes in India (including the All India Institute of Medical Sciences, Delhi, Post-Graduate Institute of Medical Sciences, Chandigarh, Sanjay Gandhi Post Graduate Institute, Lucknow, Christian Medical College, Vellore, Medanta-Medicity, Gurgaon, Madras Medical College Chennai, along with many others) along with leading experts from

TABLE 1.
Number of transplants performed in South Asia in 2019²

	India	Southeast Asia	Global
Actual DDs	715 (0.52)	1016 (0.63)	41 860 (6.88)
Actual DD after brain death	715 (0.52)	1016 (0.63)	32 861 (5.4)
Actual DD after circulatory death	(–)	(–)	8999 (1.48)
Total kidney transplants	9751 (7.12)	10 635 (6.62)	107 540 (17.67)
Deceased kidney transplants	1138 (0.83)	1698 (1.06)	65 868 (10.83)
Living kidney transplants	8613 (6.29)	8937 (5.56)	41 672 (6.85)
Total liver transplants	2592 (1.89)	2708 (1.69)	39 968 (6.57)
Deceased liver transplants	599 (0.44)	697 (0.43)	28 977 (4.76)
Living liver transplants	1991 (1.45)	2009 (1.25)	9987 (1.64)
Heart transplants	187 (0.14)	218 (0.14)	9266 (1.52)
Lung transplants	114 (0.08)	114 (0.07)	7151 (1.18)
Pancreas transplants	22 (0.02)	25 (0.02)	2508 (0.41)
Small-bowel transplants	(–)	(–)	146 (0.02)
Total organ transplants	12 666 (9.25)	13 700 (8.53)	166 579 (27.38)

Data presented in absolute number and rate per million inhabitants (pmp).
DD, deceased donor.

**FIGURE 2.** Number of international visitors in India.

Nepal, Bangladesh, Pakistan, and Sri Lanka. The various topics and authors were decided, and subsequent working group meetings were held virtually because of the coronavirus disease 2019 (COVID-19) pandemic. A final meeting was conducted in February 2022 to review and confirm the final version.

These guidelines address the pretransplant screening of donors and transplant candidates for endemic infections, posttransplant prophylaxis, and management of infections, along with travel and vaccination guidelines (Tables 2–6). Because there is a paucity of published literature specific to this region, the guidelines comprise a combination of literature review, expert opinion, and unpublished data from

leading transplant centers in this region. These guidelines will aid the transplant specialists in this part of the world as well as those elsewhere who take care of recipients who have traveled to the region.

ENDEMIC BACTERIAL INFECTIONS

Mycobacterium Tuberculosis

Background and Epidemiology

TB is highly endemic in SA, so a thorough evaluation for active infection before transplantation in recipients and donors (because it can be transmitted via the

TABLE 2.**Routine screening for potential SOT donors and recipients in South Asia**

Test	Candidate	Deceased donor	Living donor
HIV			
Fourth-generation Ag/Ab screen	Yes	Yes	Yes
NAT	No	Yes	If high-risk behavior ^{a,9}
CMV IgG antibody	Yes	Yes	Yes
EBV IgG	Yes	Yes	Yes
Hepatitis B virus			
HBsAg	Yes	Yes	Yes
Anti-HBc Ab	Yes	Yes	Yes
HBV DNA	If liver transplant	Yes	If anti-HBc+
Anti-HBs Ab	Yes	Yes	Yes
Hepatitis C virus			
Antibody testing	Yes	Yes	Yes
NAT	Yes	Yes	Liver transplant or positive antibody
Strongyloides IgG	Yes	Yes	Yes
Toxoplasma IgG (heart transplant)	Yes	Yes	Yes
Syphilis screening by enzyme immunoassay (TP-EIA) (with additional testing if positive)	Yes	Yes	Yes
Mycobacterium TB	History of close contact or past history of inadequately treated TB	NA	History of close contact or history of inadequately treated TB
TST or IGRA			
Urine culture	Yes	Yes	Yes
Blood culture	If indicated clinically	Yes	If symptoms

^aIntravenous drug users, men who have sex with men, multiple sex partners.

Ag/Ab, antigen/antibody; anti-HBc Ab, anti-hepatitis B core antibody; anti-HBs Ab, anti-hepatitis B antibodies; CMV, cytomegalovirus; EBV, Epstein-Bar virus; HBsAg, hepatitis B surface antigen; IgG, immunoglobulin G; IGRA, interferon-gamma release assay; NA, not available; NAT, nuclear acid test; SOT, solid organ transplant; TB, tuberculosis; TP-EIA, Treponema pallidum enzyme immunoassay; TST, tuberculin skin test.

TABLE 3.**Screening for infections endemic in South Asia**

Infection	Test	Screening in Candidate	Deceased donor	Living donor
Tuberculosis	TST or IGRA	History of contact or past history of inadequately treated TB	NA	History of contact or past history of inadequately treated TB
Melioidosis (regional)	Culture	No	No	No
Histoplasma	Antigen Urine	No	No	No
Penicillium marneffei	Culture	Yes, if clinical disease suspected	Defer donor	Yes, if clinical disease suspected
Sporothrix (regional)	Culture	Yes, if clinical disease suspected	Defer donor	Yes, if clinical disease suspected
Malaria	Smear and antigen test	Yes, if clinical disease suspected	Yes,	Yes, if clinical disease suspected
Leishmania (Bihar, Nepal)	Leishmania antigen/antibody	Yes, if clinical disease suspected	Yes, if suspected	Yes, if clinical disease suspected
Strongyloides	Strongyloides IgG	Yes	Yes	Yes
Hepatitis E	IgM HEV	Yes, if elevated LFTs	Yes, if elevated LFTs	Yes, if elevated LFTs
Rabies	IgM	No	Yes, if unknown encephalitis	no
Dengue	NS1 antigen/IgM	In peak season	Yes	In peak season
Leptospira	IgM	Yes, if clinical disease suspected	Yes, if suspected	Yes, if clinical disease suspected
Filariæ (North India)	Filarial antigen or micro-filariæ in blood	Yes, if clinical disease suspected	If suspecting	Yes, if clinical disease suspected

HEV, hepatitis E virus; Ig, immunoglobulin; IGRA, interferon gamma release assay; LFT, liver function test; NA, not available; TB, tuberculosis; TST, tuberculin skin test.

transplanted organ) is required. Worldwide, TB is the 13th leading cause of death and the 2nd leading infectious killer after COVID-19 (above HIV/AIDS). In 2020, an estimated 10 million people developed TB worldwide.¹⁰ SA is home to 25% of the total world population and has 40% of the global TB population. According to the India TB Report 2020, there were an estimated 2.69 million cases of TB in India, accounting for a quarter of all global

TB cases.¹⁰ TB is 20 to 74 times as frequent and carries a high mortality in SOTRs.¹¹⁻¹⁵ The reported incidence of TB in SOTRs in SA is 5.7% to 12.3%.¹¹⁻¹³ In SOTRs, atypical and insidious presentations are more frequent. About two-thirds of patients present with illness localizable to an organ. Pleuropulmonary involvement is encountered in <40% of patients, disseminated disease is seen in 20% of patients, and isolated lymph node involvement is

TABLE 4.**Infection prevention advice for SOT recipients traveling to South Asia**

Infection	Advice to travelers visiting endemic region
Tuberculosis	Use N95 masks when in the vicinity with a person with active TB, avoid prolonged and close contact with person with active TB, and avoid crowded places with poor ventilation.
Typhoid fever	Drink bottled water from a reliable source, frequently wash hands, and get vaccinated before travel to endemic area.
Leptospirosis	Avoid close contact with livestock and domestic animals. In case of high-risk scenarios, use chemoprophylaxis with doxycycline 200 mg once a week during exposure.
Melioidosis	Avoid exposure to soil and rainy water and avoid traveling to endemic regions during natural calamities like tsunami and floods.
Scrub Typhus	Protect against bite of the vector (mite) and minimize outdoor activities when visiting the endemic areas.
Mucormycosis	Avoid areas with heavy construction and moist surroundings. Air filter/AC should be regularly cleaned to prevent colonization with <i>Mucor</i> species.
Histoplasmosis	Avoid going to construction areas, being exposed to caves, and working on poultry farms.
Talaromycosis	Avoid highlands in endemic areas especially during the rainy season.
Sporotrichosis	Avoid skin-penetrating trauma or contact with cats and wear appropriate gloves during gardening activities.
Arboviruses: chikungunya, dengue, and Zika virus	Reduce skin exposure to mosquito bites with barrier methods, such as insect repellents and long-sleeved or permethrin-treated clothing, coils, and vaporizers.
Malaria	Chemoprophylaxis against malaria should be taken.
Japanese encephalitis	Travelers spending extensive time in Japanese encephalitis endemic areas are recommended to get vaccinated before travel.
Rabies	Avoid exposure to stray dogs, cats, and monkeys. Transplant recipients expecting intense exposure to rabies are advised pre-exposure rabies vaccination (0 and 7 d) and postvaccination titers should be checked.
Toxoplasmosis	Avoid undercooked meat and unwashed fruits and vegetables, which may possibly be contaminated with oocysts of <i>Toxoplasma</i> .
Leishmaniasis	Minimize outdoor activities, especially during dusk hours, when sand flies are most active. Wear protective clothing, apply insect repellent (ie, DEET) to exposed skin, use pyrethroid-treated bed nets, and spray dwellings with residual-action insecticides.
Travelers diarrhea and strongyloidiasis	Avoid drinking from unsafe sources of water and avoid swimming in streams or lakes. Frequent handwashing is advised. Any uncooked food, poorly cooked food, or food that is not fresh should not be eaten. Do not walk barefoot.
HAV and HEV	Maintain sanitation, personal hygiene, and food safety to prevent HAV and HEV infections. Impurified drinking water, including ice cubes; raw or inadequately cooked meat; inadequately washed raw salads; and unpeeled vegetables and fruits should be avoided. Boiling and chlorination of water will inactivate HEV, and it is safe to drink bottled water from reliable manufacturers. SOT recipients should receive the HAV vaccine series before travel to moderate- to high-risk infection areas, and (ideally) seroconversion should be assessed before travel.

AC, air conditioning; DEET, diethyl meta toluamide; HAV, hepatitis A virus; HEV, hepatitis E virus; SOT, solid organ transplantation; TB, tuberculosis.

seen in about 5% of patients.¹¹ A range of X-ray manifestations can be seen, including atypical nonapical and diffuse interstitial infiltrate, miliary pattern, nodules, and pleural effusions. About one-fifth present with fever of unknown origin.^{11,12}

Evaluation and Management of Prospective Donors for Active TB

Living Donors

A detailed TB screening history of living donors is mandatory, which includes symptoms of active disease and a history of TB. If a living donor is asymptomatic with a normal physical examination, usually only a screening chest X-ray is done. If there is clinical or radiological suspicion, follow-up investigations include a high-resolution computed tomography (CT) scan or approaches to get a microbiological or histological diagnosis (sputum examination, bronchoalveolar lavage [BAL], needle aspiration, or biopsy).¹⁶

Living donors with active TB should not be accepted without adequate treatment. The optimal duration of treatment in a donor is not clearly defined, but common practice in the region is to proceed with the transplant surgery

after at least 2 mo of intensive treatment with 4 drugs, including rifampicin (RIF), and documentation of clinical and radiological response. This treatment period should be extended if there is any evidence of incomplete response, either clinically or radiologically. Because of more limited dialysis facilities and the high chances of other complications in the recipient, this approach may be considered for those who do not want to wait for a full treatment, after a detailed discussion of the risks and benefits. There was consensus among experts that in such a situation, albeit rare in our region, the recipient should be given isoniazid (INH) prophylaxis for 6 mo (assuming susceptibility in the donor's strain, otherwise another agent or agents should be chosen) and should be kept under close clinical observation for evidence of TB in either the graft or elsewhere.

If the donor has multidrug-resistant (MDR) TB, then they should not be accepted before finishing the complete course of antituberculous treatment and documentation of complete remission.

Deceased Donors

Deceased donors can present more of a challenge, as a good medical history may be harder to obtain; careful evaluation of radiographs/CTs of the deceased donor

TABLE 5.**Vaccination in SOT candidates and recipients in South Asia**

Vaccine name and type	Doses and interval before transplant	Doses and interval after transplant	Comment
COVID	2 doses 4 wk apart (or as per individual vaccine recommendation)	Booster as required	Protective levels not defined
Diphtheria, pertussis, tetanus (inactivated)	Part of universal immunization One booster 10 y	Booster every 10 y	
Herpes Zoster	2 doses 4 wk apart	Contraindicated	
Live vaccine (Zostavax)	2 doses 4 wk apart	RZV can be given posttransplant	
Inactivated (RZV- Shingrix)			
Hepatitis A Inactivated	2 doses, 6 mo apart at least 8 wk before transplant	Booster not required Contraindicated after transplant	Should be given to travelers to South Asia
Live attenuated Hepatitis B Inactivated	3–4 doses before transplant, double dose in those with CKD and dialysis	Booster dose if antibody titer <10 mU/mL	Serology testing 4-wk after complete dose
Human papilloma virus Inactivated	3 doses at 0, 1, 6 mo	Should be completed after transplant if not fully vaccinated	Double dose after transplant as in CKD Females aged 11–26 y (preferable) ^a
Influenza Inactivated	Trivalent or quadrivalent—single dose Single dose at least 4 wk before transplant	1 dose annually Contraindicated after transplant	Inactivated vaccine can be given as soon as 1–3 mo after transplant
Live Measles, Mumps, Rubella Live vaccine	Should be completed 4 wk before transplant	Contraindicated	Contraindicated after transplant
Meningococcal Inactivated	2 doses, 8 wk apart in those at risk	Booster once in 5 y	Should be given before splenectomy, before eculizumab, or going on Haj
Pneumococcal Inactivated—conjugated polysaccharide	1 dose PCV-13, followed after 8 wk by 1 dose PPV23	Booster dose PPV23 after 5 y	
Typhoid Inactivated	Polysaccharide: 1 dose or conjugated: 1 dose	Polysaccharide: needs booster 3 y Booster not required	Before travel is required
Varicella Live vaccine	Pretransplant 2 doses 1 mo apart	Contraindicated	

^aEfficacy reduces significantly after 26 y but it can be given until 45 y of age.

CKD, chronic kidney disease; COVID, coronavirus disease; PCV 13, pneumococcal conjugate vaccine; PPV23, pneumococcal polysaccharide vaccine; RZV, recombinant zoster vaccine; SOT, solid organ transplantation.

TABLE 6.**Considerations for vaccines for SOT recipients traveling to South Asia**

Vaccine/type	Doses and interval after transplant	Comment
Cholera/inactivated	2 doses 1 wk apart	Complete before travel
Hepatitis A/inactivated-live	Inactivated, 2 doses, 6 mo apart Live vaccine is contraindicated	Complete before travel, consider documenting seroconversion Can give immunoglobulin for prevention
Typhoid vaccine/inactivated	Polysaccharide- Conjugated: 1 dose	Needs booster every 2 y Booster not required
Rabies/inactivated	Preexposure - 3 doses at d 0, 7, and 21 or 28 d Postexposure prophylaxis at d 0, 3, 7, and 14	Often given for higher-risk travel Immunoglobulin is required after bite along with vaccine
Japanese encephalitis/inactivated-live	2 doses 4 wk apart Live vaccine is contraindicated	Complete vaccination before travel; often only given for longer travel or to high-risk regions (UP, Bihar)
Dengue/live	Contraindicated	Take precautions against mosquito bites instead

SOT, solid organ transplantation.

may provide information about their TB status. Deceased donors with known or suspected active TB should not be accepted.¹⁶ If active TB is found in the transplanted organ, then the recipient should be initiated on full antitubercular

treatment, and recipients of other organs should be notified of the risk. Donors with a history of completed TB treatment should be further evaluated, and if either acid-fast bacillus smear or molecular tests are positive, then

they should be rejected; however, if the tests are negative or the result is pending, then donation can be considered after explaining the risk to the recipients.¹⁶ Lungs from donors with significant residual damage from prior TB should not be used for donation.¹⁷

Screening for Latent TB Infection in Donors

The World Health Organization/Centers for Disease Control and Prevention/American Society of Transplantation and other guidelines suggest testing and treatment of latent TB infection (LTBI) before transplantation.^{5,7,18} However, most SA centers do not screen donors for LTBI. The reason for not doing routine screening is that most people in SA are vaccinated with Bacille Calmette Guerin and exposed to TB, which interferes with tuberculin skin test/purified protein derivative (TST/PPD) and the other reason is that the other test, that is, TB-specific interferon-gamma release assay (IGRA, ie, QuantiFERON-TB, T-SPOT.TB) is costly and not yet validated for use in this region. The sensitivity and specificity of these tests are poor in our setting.¹⁹ The Revised National TB Control Program of India does not recommend universal screening for LTBI in the general population.²⁰ There was consensus that screening should be considered for living donors who have a history of close contact with an individual with active TB or those with a history of inadequately treated TB; however, these tests are not validated in deceased donors (Table 2).

Transplant Candidate Screening and Management of Active TB

A thorough history, including prior exposures and history of TB and a chest X-ray, should be obtained from all prospective recipients. Anyone with clinical and radiological evidence of active TB should be investigated further. Transplant candidates who develop ascites or pleural effusions should be evaluated for active TB. It is important to do adenosine deaminase and rapid molecular diagnostic tests (ie, GeneXpert/RIF) for TB in these situations because stains and cultures for acid-fast bacillus and other tests may be less sensitive and with delayed results.^{13,21}

The optimal duration of treatment for active TB before proceeding to transplant remains controversial; however, wherever possible, completion of treatment in the pretransplant period itself is recommended.²¹ This is a common practice in SA to accept these patients after 8 wk of intensive treatment with 4 drugs, including RIF, given the high cost and lack of universal availability of long-term dialysis in patients with kidney failure and critical condition of patients with liver failure. Because RIF, a cytochrome P450 3A4 enzyme inducer, accelerates the metabolism of calcineurin inhibitors (CNIs), thus raising the dose needed to maintain therapeutic levels by 3- to 4-fold, further treatment should be continued with 3 drugs, including INH, ethambutol, and either fluoroquinolones/pyrazinamide to complete 1 y of treatment. A recent study from India used a levofloxacin-based regimen (without RIF) in their patients after transplant, and they were successful in full remission in >90% of patients.²²

Screening for LTBI in Transplant Candidates

In contrast to most recommendations from the developed countries, screening for LTBI is not done in most

transplant centers in SA in asymptomatic patients with normal chest X-ray, abdominal ultrasound, and without any history of TB in close contact or history of inadequately treated TB (Table 3).

There are 2 choices for a screening test—TST/PPD and IGRA assays. The former is limited by the high likelihood of cutaneous anergy, making the test false negative even in those with latent infection; further pretransplant TST positivity had low sensitivity and specificity for predicting posttransplant TB, so this test should not be used for either screening or for diagnosis.^{19,23,24} Regarding IGRAs, there are no studies on the use of IGRAs and their predictive value in patients with kidney failure and transplant recipients in SA. Even from other regions, these studies have been largely inconclusive.²⁵

Global recommendations to screening for latent TB are based on the assumption that individuals with LTBI are at a high risk of progression to active TB after transplantation; a screening test would be reliably able to identify those with LTBI with a high degree of sensitivity and specificity, and safe and effective chemoprophylactic approaches are available. Current evidence supporting these assumptions in transplant recipients in high-endemic regions of SA is limited, and recommendations are largely expert opinions. A relatively small proportion of patients are impacted by these guidelines in high-income countries where the population prevalence of TB is low, but the implications (financial, logistic, increased burden on the health system) are significant for low-resource countries of SA with high population prevalence.

Some centers may wish to consider routine screening for LTBI preferentially using IGRA, that is, QuantiFERON-TB, T-SPOT.TB over TST/PPD. IGRA or TST/PPD should be performed in those with a history of TB in close contact or with a history of inadequately treated TB in SA. Given the public health importance of this recommendation, appropriately designed studies are needed to ascertain the positive predictive values of IGRA in kidney failure populations in this region.

Prophylaxis for LTBI

Routine prophylaxis for LTBI is not practiced in SA, given the lack of good assays to reliably identify LTBI in this population, the high prevalence of resistance to RIF or INH (the primary drugs used for LTBI treatment), and the risk of hepatotoxicity. The challenge of addressing drug-resistant TB is critical for India, because India contributes >27% of global drug-resistant TB cases. The First National Anti-Tuberculosis Drug Resistance survey in India showed that 23% of new cases had resistance to any drug, with INH resistance in 11% and 25% in new and previously treated TB cases, respectively.²⁶ Indeed, resistance to INH, the cornerstone of chemoprophylaxis, has been identified as the biggest challenge affecting TB control in India. Widespread use of INH alone is likely to further fuel resistance.²⁶ Studies from India and Pakistan show that although a standard course of INH decreases the risk of developing TB posttransplant, there is no effect on overall mortality and substantial risk of liver damage.^{27,28}

In a recent review of 41 cohort studies of LTBI prophylaxis in SOTRs, there was a reduction in the incidence of TB in patients who received prophylaxis; however, the risk of hepatotoxicity was 6% in non-liver recipients and

10.9% in liver recipients.²⁹ Further studies are required to know the benefits or harms of prophylaxis in SOTRs.

There was no consensus on the best approach to the treatment of LTBI. The proposed approaches include INH daily for 6 to 9 mo, RIF daily for 4 mo, and INH and rifapentine weekly for 3 mo.¹⁸ Liver function should be monitored regularly in all patients. Chemoprophylaxis should be initiated before transplant and can be continued posttransplant if using INH, although it should not be used after transplant if RIF-based regimen is used given its drug interactions. The panel highlighted the need for randomized controlled trials to generate evidence around the efficacy and cost-effectiveness of screening using IGRA and the treatment of LTBI among organ transplant recipients in SA.

Posttransplant Monitoring for TB

A high index of suspicion for TB after transplant is necessary, given the high incidence of TB in the region. Observational studies show a very high lifetime increase in the risk of TB in transplant recipients and the myriad, often atypical presentations, including prolonged fever.¹¹⁻¹⁵ Early use of sensitive radiological investigations (eg, CT scan) and invasive procedures to obtain specimens for microbiological or histological tests is critical in making a diagnosis.²¹ Sometimes, the diagnosis is made retrospectively after a favorable response to antitubercular therapy in cases with fevers of unknown origin.

Treatment of TB After Transplant

For the treatment of TB after transplant, standard practice is to use 4 drugs initially: INH, ethambutol, pyrazinamide, and levofloxacin for 2 to 3 mo, and later on continue with 3 drugs INH, ethambutol, and either pyrazinamide or levofloxacin to complete the treatment for 12 mo. A number of observational studies from SA have shown the efficacy of a regime in which RIF is replaced with fluoroquinolone.^{11,22,30} If possible, patients should receive the standard 4-drug treatment (including RIF); however, RIF is a potent inducer of cytochrome A 450 and can lead to a marked reduction in the levels of CNIs, thus increasing the risk of acute rejections in 30% of cases and graft loss in 20%.¹⁴ The interaction is sometimes unpredictable, and it can reduce the CNI levels by 2 to 5 times. Rifabutin can be used as a substitute for RIF if a patient is having miliary or disseminated TB, because it is a less potent inducer of CYA P 450 3A4 enzyme and found to be equally effective.³¹ The dose of rifabutin at 5 mg/kg/d is similar to RIF.

The blood levels of CNIs and mammalian target of rapamycin inhibitors should be regularly monitored in patients treated with rifamycin (RIF, rifabutin) and the doses should be adjusted accordingly. Using rifamycin as one of the drugs for the treatment of posttransplant TB would increase the cost significantly because of the high doses of CNIs/mammalian target of rapamycin inhibitors needed to maintain the levels and the requirement for frequent drug monitoring. As a result, the panel recommends a rifamycin-free regimen as the standard approach to treating posttransplant TB in this region except in special situations.

Advice to Travelers to SA

Transplant recipients should follow standard precautions if traveling to SA: use N95 masks when in the vicinity

of a person with active TB, avoid prolonged and close contact with persons with active TB, and avoid crowded places with poor ventilation. Posttravel testing with TB-specific IGRAs may be recommended for those who had higher risk exposures or longer durations of travel in endemic areas and is generally more sensitive in immunocompromised transplant recipients; however, TST may sometimes be a valid and cheaper alternative in some situations.

Typhoid (Enteric) Fever

Background and Epidemiology

Typhoid fever is caused by *Salmonella enterica* serovar *Typhi*, typically via ingestion of contaminated food or water, and presents with fever and gastroenteritis. Some regions of SA have a high incidence of typhoid fever.³² In India, the incidence is reported to be as high as 235 to 976/100 000 persons per year.³³ The United States Centers for Disease Control and Prevention reported that in 2016, 77% of cases of typhoid fever were detected after travel to India, Pakistan, and Bangladesh.³⁴ Although typhoid is not typically a latent infection, it can persist in certain individuals, such as those with gallstones.

Clinical Features and Diagnosis

After an incubation period of 2 to 3 wk, a patient usually presents with headache and high-grade fever. Gastrointestinal disturbances like abdominal pain, diarrhea (in children), or constipation are commonly observed. "Rose spots" (faint salmon-colored macules on the trunk and abdomen) may be seen in some patients during the second week of the illness.³⁵ If left untreated, the patient may develop intestinal bleeding and ileocecal perforation in the third week of symptoms leading to peritonitis and septicemia.^{36,37} Some patients might develop neurological manifestations like altered sleep patterns, acute psychosis, meningitis, and encephalopathy.^{37,38} In a series of 3 cases of *Salmonella* in renal transplant recipients, the disease course was more serious than in nonimmune-compromised patients.³⁹

Any patient with protracted fever for more than a week and who is living in or visiting an endemic region should be evaluated for enteric fever. The gold standard of the diagnosis is blood cultures with an adequate amount of blood.⁴⁰ Widal test or Typhi dot immunoglobulin (Ig) M have poor sensitivity and specificity, so they are not recommended.⁴⁰

Donor and Candidate Screening

Routine pretransplant screening of healthy donors or candidates is not recommended. There are no published reports of transmission of *Salmonella* through an organ transplant.

Management

The usual treatment of choice for *Salmonella* infections is fluoroquinolones if the isolate is sensitive; however, in SA, resistance to fluoroquinolones is seen in >80% of isolates, so it is not the preferred drug in SA.⁴¹ In the surveillance of enteric fever in the Asia project study, MDR strains (ie, resistant to amoxicillin, trimethoprim-sulfamethoxazole [TMP-SMX], chloramphenicol), were

detected in a minority of strains from India, Nepal, and Bangladesh, whereas the majority of strains from Pakistan showed MDR.⁴² The majority of the *Salmonella* isolates are susceptible to azithromycin and ceftriaxone. However, resistance to ceftriaxone (extremely drug-resistant) is increasingly being described in Pakistan.⁴³ In patients with a diagnosis of enteric fever in SA, the drug of choice is injectable ceftriaxone for 2 wk or azithromycin for 1 wk; however, in Pakistan, the drugs for enteric fever would be a combination of meropenem for 10 to 14 d along with azithromycin for 1 wk.⁴⁴ Adjuvant corticosteroids may be combined with drug treatment in patients with encephalopathy.

Prevention

There are not enough data to recommend routine vaccination against typhoid. Vaccination of transplant recipients may be considered during an outbreak. Of the 2 available vaccines, the live attenuated vaccine, Ty21a, should not be given. A typhoid conjugate vaccine, Typhar-TCV has recently been prequalified for use in several countries and can be given after transplant.⁴⁵ Vaccine efficacy in these pre- and posttransplant populations has not been studied.

Travelers to SA

Any SOTRs visiting the SA region should be advised to get vaccinated with a conjugated vaccine⁴⁵ (preferable, for a more robust immune response) or the polysaccharide vaccine against typhoid before traveling, avoid drinking water direct from a tap, pumps, or well, avoid raw produce, and wash hands frequently.⁴⁶

Leptospirosis

Background and Epidemiology

Leptospirosis is a zoonotic disease caused by the genus *Leptospira*, a pathogenic spirochete. It is endemic in SA, especially in several south and east Indian states, that is, Andaman and Nicobar, Gujarat, Karnataka, Kerala, Maharashtra, Odisha, and Tamil Nadu.^{47,48} The peak occurs in summer and epidemics after monsoons and heavy rainfall.⁴⁹ Humans acquire infection by penetration of the spirochete via abraded skin or mucous membrane.⁴⁹ Farmers, veterinarians, sewage workers, and animal handlers are at higher risk.

Clinical Features and Diagnosis

Leptospirosis should be considered as a differential diagnosis in all community-acquired febrile illnesses.⁴⁹ Myalgia, conjunctival suffusion, jaundice, hemorrhage, and acute kidney injury are common symptoms. There are reports of liver transplantation because of liver failure by leptospirosis.⁵⁰

The gold standard for diagnosis of leptospirosis is the microscopic agglutination test with a 4-fold or more rise in titers in paired samples. IgM enzyme-linked immunosorbent assay (ELISA) is a more sensitive test, which is also used for screening but may be false negative in a transplant recipient.^{48,49} Polymerase chain reaction (PCR) is more specific but not widely available in the region.⁵¹ The urine culture can remain positive for many weeks after

infection and PCR can remain positive for months, which may reflect the detection of both live and dead bacteria.⁵²

Donor and Recipient Screening and Donor's Acceptance Criteria

Routine Donor Screening in Asymptomatic Donors or Candidates Is not Recommended⁸

There is a possibility of transfusion-transmitted leptospirosis from donors with asymptomatic infection. Screening should be done if a candidate or donor has significant epidemiologic risk or exposure. Donation should be deferred for 3 mo after a donor has recovered from leptospirosis.

Management in Transplant Recipients

Treatment is as in nonimmunosuppressed population with intravenous penicillin and ceftriaxone for severe disease. Doxycycline, azithromycin, amoxicillin, or ampicillin can be used for milder cases.⁴⁹

Recipients Traveling to an Endemic Region

Travelers should avoid close contact with livestock and domestic animals, touching soil, freshwater, or objects that might be contaminated from animal urine. Chemoprophylaxis with doxycycline 200 mg once a week may be used during periods of high-risk exposure.⁵³

Melioidosis

Background and Epidemiology

Melioidosis is caused by the facultative Gram-negative rod *Burkholderia pseudomallei*, an environmental saprophyte. Melioidosis is endemic in some areas of SA: India, Nepal, Bangladesh, and Bhutan.⁵⁴ In India, the majority of cases are reported from Karnataka and Tamil Nadu.⁵⁴ Transmission can occur via cutaneous inoculation, inhalation, aspiration, and occasionally ingestion. Diabetes, chronic lung disease, chronic kidney disease, and excessive alcohol use are risk factors.⁵⁵

Few cases of melioidosis following organ transplantation have been reported and most of them are from India.⁵⁶⁻⁵⁸

Clinical Features and Diagnosis

Melioidosis is often called "the great mimicker." An acute febrile illness with pneumonia is the most common presentation. Bacteremia is seen in up to 55% to 60% of cases and is associated with higher mortality.⁵⁵ Other manifestations include visceral abscesses involving the liver, spleen, kidney and prostate, septic arthritis, osteomyelitis, and intramedullary abscess are also seen.⁵⁵⁻⁵⁹

Infection with *B pseudomallei* can be latent and subsequently reactivated, and this can pose a significant problem in organ transplant recipients during the period of heightened immunosuppression. In various case reports of transplant recipients from India, patients presented with septicemia, septic arthritis, pyrexia of unknown origin, genitourinary, and pulmonary manifestations.⁵⁶⁻⁵⁸

Screening Recommendation

Healthy donors and recipients do not need pretransplant screening; as of date, no published case has been reported

to be because of reactivation from latent focus post-organ transplant; therefore, more studies are required.

Management

Treatment is done in 2 phases—an intensive phase with beta-lactams like ceftazidime and carbapenems,⁵⁹ followed by TMP-SMX for the eradication phase. Doxycycline is an alternative for those who cannot tolerate TMP-SMX.

Prevention and Prophylaxis

Renal transplant recipients should avoid exposure to soil and water during the rainy season and should stay indoors during natural disasters like tsunamis and floods. TMP-SMX given as part of routine prophylaxis in the early posttransplant period may protect against melioidosis and could be considered in high-risk situations; however, the doses for prophylaxis have been suggested to be high.⁵⁹

Recipients Traveling to Endemic Areas

Travelers should use waterproof boots and gloves to protect against contact with soil and water in endemic areas and clean skin lacerations, abrasions, or burns contaminated with soil or surface water.⁵³ Melioidosis needs to be included in the differential diagnosis of fever of unknown origin in transplant recipients who have traveled to endemic areas.

Scrub Typhus

Background and Epidemiology

Scrub typhus is caused by an intracellular bacterium *Orientia tsutsugamushi* and transmitted by the Trombiculid mite.⁶⁰ Scrub typhus has been reported widely in India and Pakistan and is a major cause of pyrexia of unknown origin.^{60,61} Risk factors include living in rural areas, sleeping outdoors, and recent rainfall, conditions that increase the risk of mite bites.⁶⁰ Only 1 case of scrub typhus infection has been reported in a kidney transplant recipient 4 y after transplant, presenting with fever, myalgia, headache, and vomiting.⁶²

Clinical Features and Diagnosis

Manifestations include isolated fever, maculopapular rash (eschar), lymphadenopathy, liver dysfunction, pneumonitis, meningitis/meningoencephalitis, acute kidney injury, and septic shock.^{60,63} Eschars may be overlooked if present in areas that are missed on the clinical examination, like the axilla, inframammary area, groin, etc. It can cause severe disease in SOTRs.⁶² Diagnosis requires the demonstration of IgM antibodies or nucleic acid testing by PCR.⁶³

Donor and Candidate Screening

Routine screening is not recommended, because this is an acute infection, and there are no suitable tests for screening.

Management

Doxycycline is the drug of choice; longer treatment may be indicated for transplant recipients. Azithromycin, RIF, and chloramphenicol are alternative therapies.⁶³

Prevention and Recipients Traveling to an Endemic Region

Prevention strategies include protection against the bite of the vector. When visiting endemic areas, transplant recipients should avoid areas with lots of vegetation and brush where mites/chiggers may be found.⁵³

ENDEMIC FUNGAL INFECTIONS

Mucormycosis

Background and Epidemiology

Mucormycosis is an invasive fungal infection caused by *Mucorales* species, a common saprophytic fungus.⁶⁴ A heavy burden of fungal spores during construction, contaminated air filters, and healthcare-associated devices have been linked to nosocomial acquisition.⁶⁴ A review of several Indian studies revealed a prevalence rate of 0.14 cases/per 1000 population, 70 times the worldwide rate.⁶⁴ Invasive mucormycosis is among the most common invasive fungal infections in SOTRs in India.⁶⁵ Risk factors include renal failure, diabetes, prolonged neutropenia, corticosteroid use, and prior voriconazole or caspofungin use.⁶⁴⁻⁶⁸ Mucormycosis has been reported in India as a sequelae to COVID-19 infection in both the general population and kidney transplant recipients.^{67,68} The diagnosis is established by symptoms, typical imaging findings, cultures, and the presence of broad, aseptate hyphae in biopsy samples.⁶⁵⁻⁶⁷

Donor Screening

Specific testing is not done in non-lung donor; however, donor screening should be performed for lung recipients from deceased donors by pretransplant bronchoscopy specimens. The diagnosis is made by the presence of pauciseptate or nonseptate hyphae with a ribbon-like appearance in BAL samples from the lung by direct microscopy. The fungal culture is positive in only 50% of cases.⁶⁹

Candidate Screening

Routine candidate screening is not recommended. Bronchoscopy should be performed for the post-lung transplant in the recipient.

Prevention and Prophylaxis

An epidemiological history should be obtained before transplant from high-risk patients, that is, those with poorly controlled diabetes, neutropenia, or on immunosuppressive medications. Recipients should be advised to control their diabetes and to avoid areas with heavy construction and moldy surroundings.⁶⁴⁻⁶⁶ Corticosteroid doses should be kept as low as possible.⁶⁵⁻⁶⁸ Air filters and conditioners should be regularly cleaned to prevent colonization with *Mucorales* species.⁶⁴⁻⁶⁷ Posaconazole or other antifungals active against *Mucorales* species would routinely be used for recipients of donor lungs that are colonized with *Mucorales* species on pre- or posttransplant respiratory culture and may be considered in organ recipients requiring very high levels of immunosuppression.^{66,69}

Management

Wide surgical excision or debridement, reversal of underlying risk factors, along with antifungal treatment

is the mainstay of treatment.^{64,69} Liposomal amphotericin B should be used as induction therapy followed by Posaconazole or similar as maintenance therapy.^{64,68,69} The duration of treatment for invasive mucormycosis is based on clinical and radiological resolution.

Recipients Traveling to an Endemic Region

Travelers should be advised to avoid areas with heavy construction and moist or moldy surroundings.

Histoplasmosis

Background and Epidemiology

Histoplasma capsulatum infection is endemic in the northeast region and the Gangetic belt of India and is increasingly reported from other parts of SA.⁷⁰⁻⁷² *Histoplasma* thrives in a warm and humid environment such as soil enriched with nitrogenous compounds and phosphates derived from avian excreta and bat guano.⁷⁰ The infection is usually acquired through the inhalation of microconidia. Posttransplant histoplasmosis is rare, with an estimated incidence of <1%, even in endemic areas.⁷³ Transplant-associated infections surveillance network reported a 12-mo cumulative incidence rate of histoplasmosis of 0.1%.⁷³ The median duration of presentation from the time of transplant in 1 series from India was 5 y (range, 1.5–5 y).⁷¹ Most infections in western data occurred within 1 to 2 y posttransplant.

In transplant recipients, the disease may develop because of reactivation of latent infection or new exposure after transplantation. Rarely transmission can occur via transplanted organs.⁷⁴

Clinical Features and Diagnosis

The presentation is nonspecific with fever, lymphadenopathy, and nodules/infiltrate on chest imaging and can mimic TB.⁷⁰⁻⁷³ Diagnosis requires demonstration of the fungus in blood, fluid, or tissue specimens obtained by bronchoscopy or FNAC/biopsy.⁷¹⁻⁷³ In patients with disseminated infection, blood cultures using a lysis centrifugation system and *Histoplasma* antigen in urine and body fluids (BAL, cerebrospinal fluid [CSF]) can help in early diagnosis.^{8,73} Serology is not very useful for diagnosis in immunocompromised patients. Awareness of the possibility of histoplasmosis is necessary when investigating a posttransplant febrile illness in a patient from an endemic area.

Donor Screening and Acceptance Criteria

Routine screening of asymptomatic donors for histoplasmosis is not recommended, because donor-derived infection (DDI) has rarely been described, and the screening tests are not sufficiently sensitive/specific.^{75,76} Donors with active histoplasmosis are excluded from donating organs.^{5,8,75} Radiographic sequelae of old histoplasmosis are not considered a contraindication for transplant. Donors with the recent disease may be considered after treatment for 3 to 6 mo with a resolution of signs and symptoms of active disease and clearance of *Histoplasma* antigen.^{8,76}

Recipient Screening and Posttransplant Monitoring

Pretransplant screening for histoplasmosis is of limited value.^{5,8} Recipients with pretransplant histoplasmosis

should be monitored for reactivation disease. However, if they undergo organ transplant within 2 y of diagnosis, serial *Histoplasma* antigen monitoring in urine may be helpful, and secondary prophylaxis with itraconazole may be considered.^{75,76}

Prevention and Prophylaxis, Including for Recipients Traveling to Endemic Areas

Because histoplasmosis is acquired from the environment, posttransplant patients should be advised to avoid construction areas, exposure to caves, and working on poultry farms in endemic areas. Primary prophylaxis is not recommended after organ transplant.^{5,76}

Management

Mild to moderate localized disease is treated with itraconazole. Severe disease is treated initially with liposomal amphotericin B followed by itraconazole. The minimum duration of treatment of posttransplant histoplasmosis is 12 mo, guided by clinical and radiographic responses.^{75,76}

Talaromycosis

Background and Epidemiology

Talaromycosis (formerly penicilliosis) is caused by dimorphic fungus *Talaromyces marneffeii*, endemic in Southeast Asia and Northeast India.^{72,77} Human infection occurs via inhalation of *T marneffeii* spores found in infected soil, often associated with bamboo rats.⁷⁷ The infection is seen in people living in highland areas in the endemic regions because of occupational exposure to crops or livestock or those traveling to farming areas.⁷⁸ The disease increases in rainy seasons and is associated with high mortality in organ transplant recipients.^{78,79}

Clinical Features and Diagnosis

Manifestations are similar to histoplasmosis and TB, for example, fever, weight loss, cough, anemia, lymphadenopathy, and hepatosplenomegaly.^{77,79} Skin lesions are seen only in 30% to 60% of patients, and biopsy can help with diagnosis.^{77,78} Blood cultures can take up to 2 wk to grow. Immunoassays for rapid diagnosis are under development.

Pretransplant Donor and Candidate Screening

Screening is not recommended in asymptomatic individuals, because there is no good screening test. Those living in endemic areas who have chronic skin or lymphocutaneous lesions should undergo a biopsy.^{8,76}

Prophylaxis

Primary prophylaxis has no role; however, secondary prophylaxis with itraconazole can be given for 6 to 12 mo.⁷⁶

Management

Treatment requires the use of amphotericin B lipid formulation for 2 wk (4–6 wk for central nervous system [CNS] disease), followed by oral itraconazole for a minimum of 10 wk.^{75,76}

Recipients Traveling to Endemic Areas

Travelers to endemic regions should be advised to avoid highlands and soil, especially during the rainy season.⁵³

Sporotrichosis

Background and Epidemiology

Sporotrichosis is a subacute or chronic subcutaneous, granulomatous mycosis caused by *Sporothrix schenckii* or *S globosa* and is common in SA.^{72,80} Hay, corn stalks, and soil are possible sources, and infection occurs after direct contact after minor trauma or direct inhalation.⁸⁰ Infected cats can also be a potential source of infection. Epidemics of sporotrichosis have been reported in Africa, mainly because of sapronotic transmission in miners and farmers.⁸¹ In India, sporotrichosis is common in the sub-Himalayan area of Himachal Pradesh in the north and West Bengal and Assam in the east.^{82,83} SOTRs can develop severe disseminated sporotrichosis.⁸⁴

Clinical Features and Diagnosis

Lymphocutaneous disease (skin lesions, ulceration, and lymphadenopathy) usually develops 2 to 4 wk after exposure. Other manifestations include conjunctivitis, uveitis, and hematogenous dissemination to the lung, CNS, and bone marrow in severe cases.^{80,84}

The diagnosis is established by the identification of *Sporothrix* in infected tissue on microscopy or tissue culture. Serological ELISA test using the *Sporothrix schenckii* Con A-binding fraction has proven effective for the detection of IgG antibodies in the serum of patients with cutaneous sporotrichosis with high sensitivity and specificity rates of 90% and 80%, respectively; however, there are little data in sensitivity and specificity of these tests in transplant recipients.^{80,84}

Pretransplant Donor and Candidate Screening

Routine screening is not recommended in asymptomatic individuals. Donors or candidates from endemic regions with the presence of chronic skin or lymphocutaneous lesions should be screened with histopathology and culture of tissue biopsy.^{8,76} Newer antibody-based tests can be used if available.

Management

Systemic, pulmonary, or CNS disease should be treated with a lipid formulation of amphotericin B for 4 to 6 wk, followed by therapy with oral itraconazole for a minimum of 12 mo.^{75,80} Mild infections can be treated with itraconazole. Terbinafine and potassium iodide solutions are alternatives.⁸⁰ The duration of therapy and the need for secondary prophylaxis depends on clinical and radiological improvement.

Recipients Traveling to Endemic Areas

Recipients should be advised to avoid skin-penetrating trauma or contact with cats and to wear gloves during gardening activities.⁷⁵

ENDEMIC VIRAL INFECTIONS

Endemic viral infections are common and very challenging to treat, especially in immunocompromised patients.

In this section, we will cover some of the more common pathogens, although, in the right clinical setting, consideration should be given to additional emerging pathogens such as Nipah (primary from contact with pigs or bats), the tick-borne *Nairovirus* (which causes Crimean-Congo hemorrhagic fever), and other viruses. Measles is common and should be prevented by prior disease or pretransplant vaccination.

Arboviruses: Chikungunya, Dengue, and Zika Virus

Background and Epidemiology

Chikungunya virus, dengue virus, and Zika viruses are endemic in the region and transmitted by urban *Aedes* species, predominantly *Aedes aegypti* and *Aedes albopictus*.⁸⁵⁻⁸⁸ Dengue seroprevalence studies from India and Sri Lanka have shown a positivity rate of 43% to 57%.^{85,86} Zika outbreaks have been reported in Kerala, Rajasthan, Madhya Pradesh, and Uttar Pradesh.⁸⁸ In addition to acquisition in the community, these infections can be transmitted from the transplanted organ.⁷ Perioperative dengue transmission has been described in both liver and kidney transplant recipients in India; however, it is not common.^{89,90} The recipients with DDI had difficult posttransplant courses with prolonged hospitalization and the need for intensive care unit stay and platelet transfusions.^{89,90}

Clinical Features and Diagnosis

Arbovirus infections present with acute febrile illness, along with rash, myalgia, arthralgia headache, nausea, vomiting, and conjunctival injection.^{85,87,88} Arthralgia is universal and severe in the chikungunya virus.⁹¹ Dengue fever is associated with transaminitis, leukopenia, thrombocytopenia, hemorrhage, and shock.^{90,92} Systemic involvement (meningoencephalitis, respiratory failure, myocarditis, renal and hepatic failure) is seen in severe chikungunya.⁹¹ Zika is usually associated with mild disease; however, it can lead to microcephaly in newborns born to mothers infected during pregnancy and Guillain-Barre syndrome.⁸⁸ SOTRs have higher chances of severe infection and death from acute dengue infection.⁹³ In a large series, mortality was not increased in kidney transplant recipients with chikungunya virus infection.⁹⁴

Positive nonstructural 1 antigen is diagnostic for dengue but is present only in the first 5 to 7 d of illness.⁹² IgM antibodies against arboviruses take 3 to 7 d to develop and remain in circulation for almost 4 to 12 wk.^{91,92} Serological diagnosis of dengue, Chikungunya, and Zika can be made using IgM, but it is less sensitive and specific. PCR tests are the most sensitive and specific and should be used within 7 d of symptoms onset.^{91,92,95}

Donor and Candidate Screening

Routine screening is not recommended in asymptomatic individuals or those without a recent history of fever because the donor-derived infection is uncommon; however, because disease transmission is periodic/seasonal, donor screening for dengue nonstructural 1 antigen should be done during periods of high disease activity.^{6,90,95} In patients with a recent history of fever, it is prudent to wait 2 wk and reassess before proceeding with the evaluation. The initial screening within 7 d should be done by PCR or antigen testing and after 7 d with IgM antibodies against the specific virus.⁹⁵

Donor Acceptance Criteria

If a donor is confirmed to have any of these arboviral infections, deferral is recommended for 30 d for dengue and chikungunya and 120 d for Zika.^{6,95} Organs from deceased donors with signs and symptoms suggestive of recent arbovirus infection (<30 d) should be discarded.^{6,95}

Prevention and Prophylaxis, Including for Recipients Who Travel to SA

Vaccine options are limited for these infections. Dengue vaccine (Dengvaxia) has not yet been approved in SA, and given that it is a live attenuated vaccine, it is not advised in transplant recipients. There are no approved vaccines for the chikungunya virus and Zika virus. Recipients traveling to SA should reduce skin exposure to mosquito bites with barrier methods by wearing long-sleeved or permethrin-treated clothing and using insect repellents such as N, N-diethyl-meta-toluamide or picaridin.⁵³ (Table 4)

Management

There is no specific therapy for these viruses other than adequate hydration and supportive care.

Japanese Encephalitis

Background and Epidemiology

Japanese encephalitis virus (JEV) is a flavivirus and the main cause of viral encephalitis throughout SA, with an estimated 60 000 to 70 000 clinical cases every year.^{96,97} Transmission is through mosquito bites (*Culex*) through a zoonotic cycle with pigs, birds, and horses. JEV has rarely been reported in organ transplant recipients.⁹⁸ There is a possibility of DDI, because it has been reported from blood transfusions, and other similar donor-derived viral encephalitides have been described.^{99,100}

Clinical Features and Diagnosis

JEV should be suspected in anyone presenting with a short history of febrile illness and altered mental status.^{96,97} Clinically, it is difficult to differentiate from other causes of encephalitis/encephalopathy. The ideal method for laboratory confirmation is by testing CSF or serum for JEV-specific IgM antibody.¹⁰¹ The JEV-specific IgM antibody capture ELISA (MAC-ELISA) has now become the first-line diagnostic assay recommended by World Health Organization for the detection of acute infections. The turnaround time of the IgM ELISA capture assay is a few hours. Sensitivity of IgM is 60% to 90%.¹⁰² There may be cross-reactivity with other infections. The quantitative PCRs are useful molecular assay tests because they are very specific, sensitive, and can detect low viral copies in acute or early phases of infection.¹⁰² A plaque reduction test can also be required sometimes to differentiate the JEV from other flaviviruses.^{101,102} The case-fatality rate among those with encephalitis can be as high as 30%, and permanent neurologic or psychiatric sequelae can occur in 30% to 50% of survivors.^{96,97}

Donor and Candidate Screening

Routine screening of donors for JEV is not recommended because of rare case reports of donor-to-recipient

transmission and the unavailability of a very sensitive test, because sensitivity of IgM is 60% to 90%, and there can be cross-reactivity with other infections sometimes¹⁰¹; however, in regions experiencing outbreaks the screening could be helpful in patients undergoing organ transplants because the turnaround time is short. Organ donation is contraindicated from a person suffering from encephalitis.^{5,7}

Prevention and Prophylaxis

The prevention of JE is based largely on mosquito control and immunization. Of the 4 available JE vaccines, JENVAC, an inactivated Vero cell-derived vaccine, has been shown to be highly effective against all known strains of JEV.¹⁰³ The seroconversion rates are close to 90% in the immunocompetent, although it has not been studied in transplant recipients.

Management

There is no specific therapy for JE. A number of antiviral agents have been investigated, but none has convincingly been shown to alter the outcome of JE.⁶⁸

Recipients Who Travel to an Endemic Region

All travelers to Japanese encephalitis-endemic areas should take precautions to avoid mosquito bites. Personal preventive measures include the use of mosquito repellents, long-sleeved clothes, coils, and vaporizers. Travelers planning to stay for long durations in JE endemic areas should be vaccinated with a nonlive viral vaccine before traveling.

Rabies

Background and Epidemiology

SA, and in particular India, has the highest burden of rabies deaths in the world (approximately 20 000/y), accounting for approximately one-third of the global rabies death toll.¹⁰⁴ The virus is inoculated into humans through the saliva or bites or scratches from an infected animal (often stray dogs), and then the virus spreads through retrograde transport along with nerve roots and infects the central nervous system.¹⁰⁵ This process may take weeks to months. Transmission via organ transplant has been reported with organs procured from a single donor leading to infection in multiple recipients.¹⁰⁶

Clinical Features and Diagnosis

Any patient who comes with a history of altered mental status should be evaluated for rabies. Given that the animal bite(s) could have been minor and in the remote past, the history may not be forthcoming. Rabies should be considered in the differential diagnosis of any encephalitis in SA. The demonstration of rabies antibody in the serum or in CSF, in the absence of a history of vaccination for rabies, is indirect evidence of rabies infection.¹⁰⁷ However, negative serological tests do not rule out rabies. The viral antigen may also be detected by immunofluorescence antibody test (IFAT) or PCR from the skin biopsy from the posterior region of the neck (at the hairline) of the infected patient.¹⁰⁷ Virus RNA may also be isolated from the saliva, tears, or CSF.^{8,107} Demonstration of virus antigen through fluorescent antibody testing in brain biopsy

specimens (which are largely obtained post-mortem) is the gold standard.¹⁰⁸

Donor and Recipient Screening

Routine testing of the donor and recipient for rabies is not indicated. Deceased donors admitted with a history of altered sensorium or unknown cause of encephalitis should not be accepted as donors.^{5,7,8}

Management and Postexposure Prophylaxis

There is no specific treatment for rabies. Postexposure prophylaxis consists of rabies vaccine and either anti-rabies immunoglobulin or more recently introduced monoclonal antibody.¹⁰⁸ A neutralizing antibody level of ≥ 0.5 International Units (IU)/mL of serum suggests a positive protective antibody response to vaccination. Vaccine efficacy may be decreased in transplant recipients.^{8,108}

Recipients Traveling to SA

Recipients should avoid exposure to stray dogs, cats, and monkeys. SOTRs expecting to be in situations where they could be exposed to the virus should receive rabies vaccination of 3 doses on days 0, 7, 21, or 28.¹⁰⁹ Postvaccination titers should be checked, given the potential for a diminished response. For those who have not had a preexposure vaccine, immunoglobulin, and the complete vaccine course should be given as postexposure prophylaxis, regardless of the severity of the bite or animal status.^{108,109}

ENDEMIC PARASITIC DISEASES

Malaria

Background and Epidemiology

Malaria, an *Anopheles* mosquito-borne parasitic tropical disease caused by *Plasmodium vivax*, *falciparum*, *ovale*, *malariae*, and *knowlesi*, is endemic in SA. India contributes to 4% of the total global burden of malaria cases.¹¹⁰ Many cases of malaria in organ (mostly kidney) transplant recipients have been described, including transmission from the donors.¹¹¹⁻¹¹³

Clinical Features and Diagnosis

Malaria typically presents with high-grade fever and chills.¹¹⁴ Transplant recipients may present with complications of malaria, like severe anemia, thrombocytopenia, encephalopathy, respiratory failure, or renal failure.^{115,116} The severity of malaria in transplant recipients depends upon the infecting species, level of parasitemia, organ transplanted, level of immune suppression, and delays in diagnosis and treatment.¹¹⁶⁻¹¹⁸ The outcome of organ transplant recipients is varied, with some studies quoting good outcomes whereas others did not.¹¹⁵⁻¹¹⁸

Modes of Acquiring Malaria for Organ Transplant Recipients

Organ transplant recipients can acquire malaria through (1) the transplanted organ (from the parasitized red blood cells in the vasculature or reactivation of hypnozoites from donor liver),^{115,118} (2) transfusions from blood donors with asymptomatic parasitemia, (3) reactivation and recrudescence,¹¹⁸ and (4) de novo infection in the recipient.

Donor and Recipient Screening and Acceptance Criteria

Malaria screening is usually done for all symptomatic febrile patients in SA. Giemsa-stained thick smear is the standard test for diagnosis. Rapid diagnostic techniques based on parasite antigens have varied sensitivity and specificity with an average level of detection of 200 parasites per microlitre.¹¹⁴ Molecular diagnostics like real-time PCR are more sensitive and can be used to detect parasitemia missed by smear examination and are recommended in highly endemic regions to detect asymptomatic parasitemia.^{5,7,8}

The cost-benefit ratio of routine screening of donors and recipients is unknown. Screening is advisable in patients from highly endemic areas; however, this needs more study.

All donors and candidates should be deferred for 3 mo after treatment of infection in an endemic region.^{8,118}

Posttransplant Monitoring

Periodic clinical and laboratory monitoring could be done (best with PCR tests) prospectively for 2 mo post-transplant in endemic areas, especially during periods of increased disease transmission. Preemptive therapy is not recommended but may be considered if there is a high risk of donor-derived infection.⁷

Recipients Who Travel to an Endemic Region

Recipients traveling to malaria-endemic regions should use insect repellents, wear long-sleeved clothing, avoid outdoor activities, and sleep in a well-screened room or under mosquito netting (Table 4). Recipients traveling from nonendemic to the endemic region should take chemoprophylaxis (doxycycline, atovaquone/proguanil, mefloquine, and tafenoquine).⁴⁶ Clinicians should be aware of the potential for transplant drug interactions and QT prolongation.

Toxoplasmosis

Background and Epidemiology

Toxoplasma gondii, a ubiquitous parasite present in a wide variety of animals such as birds and livestock, can be transmitted through ingestion of food, water, vegetables, and fruits contaminated with oocysts shed from cats or by ingesting tissue cysts from raw or undercooked meat.¹¹⁹ Seroprevalence studies in SA have found positivity rates of 20% to 63% in the general population.^{120,121}

Toxoplasma gondii is an important opportunistic infection in SOTRs, particularly heart transplant recipients.^{116,118} Toxoplasmosis occurring in the first 3 mo posttransplant is likely donor-derived, whereas those occurring >3 to 6 mo are because of reactivation of latent disease or de novo infection enhanced by immunosuppression.¹²² The risk depends upon the seropositivity of the donor and recipient and the use of chemoprophylaxis. In the *Toxoplasma* IgG donor-positive, recipient-negative (D+/R-) situation, transmission is highest with heart transplantation without prophylaxis (50%–75%) but can occur with other organ transplants.^{118,122}

Clinical Features and Diagnosis

Often asymptomatic in immunocompetent individuals, toxoplasmosis can present in transplant recipients with,

fever, dyspnea, cough, headache, confusion focal neurological signs, and lymphadenopathy.^{122,123} Patients can have cerebral abscesses, encephalitis, myocarditis, pneumonitis, chorioretinitis, multiorgan involvement, and disseminated disease.¹²³ The diagnosis can be made by IgM antibody or by PCR in blood body fluids, that is, bone marrow, CSF, BAL fluid, or biopsy specimens.^{123,124} The late seroconversion among transplant recipients limits the diagnostic accuracy of IgM for the diagnosis of acute toxoplasmosis in this population.^{5,124}

Donor and Recipient Screening and Acceptance Criteria

Both donor and recipient should be screened for latent infection by serology using *Toxoplasma* IgG antibody, mainly for heart and heart-lung transplants.⁵ A seropositive donor is not a contraindication to transplant; however, it defines the risk of transmission and the need for prophylaxis posttransplant.

Prophylaxis and Prevention (Including Travel)

With high-risk (D+ R-) transplants, chemoprophylaxis with TMP-SMX (160–800 mg) daily or thrice weekly (as given for *Pneumocystis jirovicii*) is effective.¹²⁴ Alternatives include a combination of clindamycin, pyrimethamine, and leucovorin; atovaquone; or dapson plus pyrimethamine.¹²⁴ The duration of prophylaxis is not well defined but should be given for at least 3 mo posttransplant.^{5,124} Lifelong prophylaxis is recommended in high-risk heart transplant recipients.

All SOTRs, whether traveling or at home, should avoid consuming raw or poorly cooked meat, untreated water (which may contain *Toxoplasma* cysts), and unwashed fruits and vegetables that could be contaminated with animal feces containing oocysts of *Toxoplasma*.⁴⁶ They should use disposable gloves for all soil and sand contacts and wash their hands after removing gloves. They should not change the litter box of indoor cats and should avoid handling stray cats and kittens.¹²²

Management of Active Infection

Treatment of active disease includes pyrimethamine, sulfadiazine, and folinic acid (leucovorin) for a minimum of 6 wk, followed by chronic suppressive therapy with the same medications at reduced doses or treatment doses of TMP/SMX.^{123,124} Alternative agents include combinations of clindamycin, atovaquone, and azithromycin. Lifelong secondary prophylaxis is needed, because treatment is effective against the proliferative tachyzoite form but not the encysted parasite.¹²⁴

Leishmaniasis

Background and Epidemiology

Leishmaniasis is caused by the protozoan *Leishmania* spp. and is transmitted by the female sandfly *Phlebotomus argentipes*. Leishmaniasis presents as cutaneous, mucocutaneous, or VL.¹²⁵ Cutaneous leishmaniasis is caused by *Leishmania major* and *Leishmania tropica* in the Middle East and central Asia and *Leishmania braziliensis* complex and *Leishmania mexicana* in America.¹²⁵ VL (also known as the kala-azar disease) is caused by *Leishmania*

infantum, *Leishmania infantum chagasi*, and *Leishmania donovani* complexes.¹²⁵

India (Bihar and Eastern Uttar Pradesh), Nepal, and Bangladesh are endemic areas for VL and contribute significantly to the global burden of VL, although the incidence had been declining during the last decade.^{126,127} VL is the predominant form in SOTRs, most frequently in kidney recipients.¹²⁸ Infection can be de novo, donor-derived or reactivation of prior infection. Recently, a case of donor-acquired leishmaniasis was described in a liver recipient; the patient responded to treatment and got better.¹²⁹

Clinical Features and Diagnosis

Leishmania spp. can cause asymptomatic infection and then remain dormant in the host for many years, becoming clinically apparent during periods of immunosuppression.¹²⁸ VL presents as fever, weight loss, hepatosplenomegaly, and pancytopenia. Atypical presentations can also be seen.^{128,130} Immunocompromised individuals have higher chances of clinical disease and severe disease compared with immunocompetent individuals or donors who are mostly asymptomatic without visceromegaly or cytopenias.¹³¹

Demonstration of *L donovani* bodies in the bone marrow and splenic aspirate remains the gold standard for diagnosis.¹²⁴ Serological assays like ELISA, indirect IFAT, and rapid tests, such as the immunochromatographic and direct agglutination test, are most widely used; however, they can be false-positive.¹³² Leishmanial antigens can be detected in serum or urine samples with a wide range of sensitivity and specificity. The usefulness of this detection method in the transplant recipient population remains to be determined. Sensitivity and specificity vary according to the method, antigens used, and geographical area.¹³² *Leishmania* PCR in bone marrow aspirate and whole blood buffy coat is more sensitive and can identify the species.

Candidate and Donor Screening and Acceptance Criteria

Transplant candidates and donors with active disease should be fully treated before transplant.^{5,6} Routine testing of donors and transplant candidates is not recommended.¹³² All donors undergo routine abdominal ultrasounds. Those with hepatosplenomegaly should be further evaluated for liver disease and chronic leishmaniasis if they have recent history of fever or any hematological abnormality (pancytopenia), in which case a bone marrow aspiration and biopsy is recommended.

Management

The standard regimen for immunosuppressed patients consists of liposomal amphotericin B 4 mg/kg/d on days 1 to 5, 10, 17, 24, 31, and 38 (total dose of 40 mg/kg).¹³³ There is no evidence that SOTRs need higher doses or secondary prophylaxis, as with HIV-coinfected patients with low CD4 counts. A temporary reduction in immunosuppression is also recommended during active treatment.¹³² Conventional amphotericin B deoxycholate is also effective but carries greater toxicity.¹²⁴

Posttransplant Monitoring

VL can relapse after transplantation in patients known or suspected to have VL pretransplant. These patients should be monitored clinically for any signs of VL. PCR monitoring is not routinely recommended; however, it should be done in those with relapse or partial improvement, because relapse is common in immunocompromised individuals.^{6,128}

Recipients Who Travel to an Endemic Area

When visiting endemic areas, transplant recipients should minimize outdoor activities, especially during dusk hours, when sandflies are most active. These individuals should also wear protective clothing, apply insect repellent to exposed skin, use pyrethroid-treated bed nets, and spray dwellings with residual-action insecticides.^{46,133}

Cryptosporidiosis

Background and Epidemiology

Cryptosporidium, an intracellular protozoan parasite is ubiquitous in natural water sources. Infection can be acquired through contaminated food or water, leading to diarrheal illness.¹²³ *Cryptosporidium* is a common cause of diarrhea in SOTRs in SA, with a prevalence as high as 16% to 53% in various studies.¹³⁴⁻¹³⁶

Clinical Features and Diagnosis

The clinical presentation may vary from asymptomatic oocyst passers to those with profuse and prolonged diarrhea associated with nausea, vomiting, abdominal pain, and fever.¹³⁴⁻¹³⁷ Dehydration, hypotension, and sometimes tacrolimus toxicity may lead to acute kidney injury.^{134,135} The extraintestinal atypical manifestations may present as respiratory tract disease, pancreatitis, and cholangitis.^{137,138}

Stool examination for identifying oocysts is the main diagnostic tool for *Cryptosporidium* infection. However, it has low sensitivity if the concentration of oocysts is low.¹³⁷ Modified staining with Ziehl-Neelsen or fluorescent techniques such as auramine-rhodamine improves detection rates.¹³⁹ Direct immunofluorescence offers the highest sensitivity and specificity and is commonly used. ELISA kits are available with sensitivities ranging from 66% to 100% with excellent specificity.^{137,138} Multiplex PCR assays can detect different gastrointestinal pathogens and significantly increase the diagnostic yield. However, their use is limited by high cost and low specificity as they cannot differentiate between asymptomatic colonization and invasive infection.^{139,140}

Donor and Recipients Screening

Screening is not routinely recommended for *Cryptosporidium*; however, in symptomatic donors, candidates, or recipients, it is advisable to test and treat if positive.¹⁴⁰

Management

Cryptosporidiosis can be hard to cure. Oral or intravenous rehydration is the mainstay of management. Reduction of immunosuppression may help in the clearance of parasites.^{134,140} Nitazoxanide is approved for treating cryptosporidiosis; the recommended dose in SOTRs is

500 mg twice daily for 14 d. However, there are no data from randomized trials on SOTRs, and they may need longer or repeat therapy.^{140,141} Combinations of antiparasitic agents such as azithromycin and nitazoxanide may be effective in refractory cases.¹⁴¹

Prevention and Recipients Traveling to Endemic Areas

SOTRs should avoid drinking untreated water and be careful when swimming in streams, lakes, or pools.^{46,140} *Cryptosporidium* oocysts are resistant to chlorine disinfection and survive for days in treated recreational water despite adequate chlorination. Drinking water should either be treated properly, filtered by <1 μm filters, or bottled water should be used.⁴⁶ Handwashing is strongly encouraged for everyone, including other family members. Contaminated food preparation surfaces should be cleaned thoroughly.

Strongyloidiasis

Background and Epidemiology

Strongyloidiasis is endemic in SA, with infection rates of 11.2% in India, and 29.8% in Bangladesh.¹⁴² Primary infection occurs through contact of skin with soil infected with human feces containing *Strongyloides stercoralis* filariform larva. The larvae travel to the lung via the venous system and from there, they move to the pharynx/trachea and then reach the gut through swallowing and become adult parasites.¹⁴⁰ In the gut, they reproduce and become rhabditiform larvae, which are then excreted through the stools. Some rhabditiform larvae may develop into filariform larvae in the intestinal lumen and penetrate the colonic mucosa or perianal skin. These filariform larvae are capable of completing a new cycle in host. This process is known as autoinfection and is unique to *S stercoralis*.¹⁴² Autoinfection plays an important role in the maintenance of long-term infection, hyperinfection syndrome, and disseminated disease in immunocompromised individuals.¹⁴³ Disease in transplant recipients may be from reactivation of asymptomatic infection (more common), donor-derived, or de novo infection.^{144,145}

Clinical Features and Diagnosis

Strongyloides stercoralis infections in humans range from asymptomatic infection to chronic symptomatic strongyloidiasis; however, in immunocompromised individuals, the disease can become disseminated (hyperinfection), with a very high mortality.^{143,144} In hyperinfection syndrome, the parasite undergoes uncontrolled proliferation, and dissemination and the larvae migrate to the lungs from the small bowel through the venous system and onto the small bowel resulting in symptoms like fever, breathlessness, hemoptysis, respiratory distress, anorexia, nausea, vomiting, diarrhea, vomiting, ileus obstruction, and gastrointestinal bleeding.¹⁴³⁻¹⁴⁵ Intestinal disease, sometimes with ulceration, may result in bacterial translocation leading to bacteremia and sepsis.¹⁴⁶ Mortality reaches up to 50% in hyperinfection syndrome and up to 70% in disseminated diseases.¹⁴³⁻¹⁴⁶ The median time of infection after transplantation was about 3 mo in a large series but it can occur at any time.¹⁴⁵ Peripheral eosinophilia, usually in immunocompetent individuals, may be absent in those on corticosteroids. Diagnosis is made by demonstration of eggs or rhabditiform larva in stool, sputum,

or duodenal aspirate. Sometimes multiple stool examinations are required to make a diagnosis. Serological tests are moderately sensitive; however, when negative, they should not be used alone to exclude a diagnosis of strongyloidiasis in SOTRs.^{147,148} Stool multiplex PCR testing increases the diagnostic yield; however, it can detect multiple and sometimes bystander gastrointestinal pathogens.¹⁴⁸

Donor and Candidate Screening

Donors and candidates should be screened before transplant in endemic areas.^{5,140} ELISA IgG is the preferred method of screening, because the sensitivity of stool examination is low. Infected donors, candidates, and recipients of organs from infected donors should be treated with ivermectin before transplantation or as soon as possible after transplantation.^{6,140} Pretransplant treatment for the living donor and recipient can be beneficial and cost-effective. The treatment can continue posttransplant in high-risk population.

Management

Ivermectin is the drug of choice for the treatment of strongyloidiasis. The dose is 200 µg/kg for 2 d, and it should be repeated once after 2 wk.¹⁴⁰ Albendazole 400 mg twice daily for 3 to 7 d or thiabendazole (25 mg/kg/d) for 3 d can be used as an alternative. Thiabendazole has been found to be more effective than albendazole and equally effective as ivermectin; however, it has more gastrointestinal adverse effects.¹⁴⁹ For hyperinfection syndrome, ivermectin should be given daily for at least 2 wk or until documented clearance (whichever is longer), along with a reduction in immunosuppression.^{140,144} In patients with severe or disseminated disease, ivermectin can be combined with albendazole.¹⁵⁰ Patients who do not tolerate oral therapy can be given either subcutaneous (preferable) or rectal preparation of ivermectin.^{151,152}

Recipients Traveling to Endemic Areas

All patients with SOT visiting endemic regions should wear shoes and follow good sanitation practices, including bottled or boiled water. After visiting the endemic region, a single dose of ivermectin may be given empirically to SOTRs.⁴⁶

Filariæ

Background and Epidemiology

Filariæ are tissue-based nematodes that grow in the subcutaneous tissue and lymphatic vessels. Lymphatic filariasis, in which the adult worms of *Wuchereria bancrofti* are found in the lymphatic system, is endemic in India (Uttar Pradesh, Bihar, Jharkhand, Orissa, Kerala, and Gujarat), Nepal, and Sri Lanka.¹⁵³⁻¹⁵⁵ It is transmitted by mosquitoes of the genera *Culex*, *Mansonia*, and *Anopheles*. Approximately half of the 120 million global cases are seen in Southeast Asia.¹⁵³ India harbors nearly 40% of all cases of infection with lymphatic filariasis in the world.^{154,155} Filariasis in SOTRs can be acquired through the donor organ or develop de novo.^{156,157} DDI is rare and only 1 case report has been described.¹⁵⁷

Patients with either DDI or an immediate diagnosis after transplantation responded well to treatment,

indicating that immunosuppression may not lead to more complications.^{156,157}

Clinical Features and Diagnosis

The disease spectrum can range from asymptomatic infection to episodes of lymphadenitis, lymphangitis, orchitis, funiculitis, or epididymitis, along with fever.¹⁵⁴ Long-standing obstruction of lymphatic vessels may lead to hydrocele, chyluria, or elephantiasis. The diagnosis is established by detection of circulating filarial antigen (for *W bancrofti* infection only), demonstration of microfilariae or filarial DNA in the blood, or adult worms in the lymphatics.¹⁵⁴ Scrotal ultrasound may reveal movements of adult worms in otherwise asymptomatic males.¹⁵³

Donor and Candidate Screening and Acceptance

Screening is usually not performed in asymptomatic donors or candidates; however, in those with clinical suspicion, screening should be done with filarial antigen in blood or a PCR-based test, which is very sensitive. Those with the active disease must be treated fully before transplant.

Management

Treatment consists of either a 2-drug regimen of diethylcarbamazine plus albendazole or ivermectin and albendazole.¹⁵⁴ Recent studies have shown that a 3-drug combination including diethylcarbamazine, ivermectin, and albendazole is better than the 2-drug combination of diethylcarbamazine and albendazole/ivermectin.¹⁵⁸

Recipients Living In or Traveling to Endemic Areas

Transplant recipients should be advised to take precautions against mosquito bites.

VIRAL HEPATITIS

Viral hepatitis is endemic in the SA region and is commonly caused by 4 hepatotropic viruses: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis E virus (HEV).

Hepatitis A Virus

Background and Epidemiology

HAV infection is an acute, usually self-limited infection caused by a nonenveloped RNA virus of the picornavirus family, which is transmitted by the fecal-oral route. HAV infection is highly endemic in SA.¹⁵⁹ By 18 y of age, 90% of the population is seropositive for HAV in India and Pakistan.¹⁵⁹⁻¹⁶¹ HAV accounts for 50% to 60% of cases of acute viral hepatitis in children. However, the case-fatality rate is higher in patients aged >50 y compared with younger adults.¹⁵⁹⁻¹⁶¹ In a series of liver transplants in patients with acute liver failure (ALF), HAV was a common cause, occurring in 21 patients (15%), with outcomes comparable with other causes. No survivors in 10 y had chronic hepatitis A in this series.¹⁶²

Screening of Donors and Candidates; Acceptance Criteria

All transplant candidates with liver test abnormalities should undergo serology testing for acute HAV

(anti-HAV IgM).⁵ Asymptomatic donors are not routinely tested for anti-HAV IgM. There are no reports of the donor-to-recipient transmission of HAV.⁶ Donors who have resolved hepatitis related to acute HAV can be accepted as usual donors.⁵

Prevention and Treatment

All transplant candidates >1 y of age at risk for HAV (ie, no history of natural disease or who are seronegative) should be vaccinated before transplantation. Two doses of the monovalent HAV vaccine or 3 doses of the combined hepatitis A and B vaccine can be taken (Table 5). Vaccination after transplantation elicits lower antibody titers and provides a shorter duration of protective immunity. Treatment of HAV in SOT is largely supportive.

Recipients Living in or Traveling to SA

Immunocompromised and nonvaccinated individuals are at high risk of acquisition of HAV infection. Maintaining sanitation, personal hygiene, and food safety are paramount in preventing HAV infection.⁴⁶ SOTRs should receive the HAV vaccine series before traveling to moderate- to high-risk infection areas.⁵³ Ideally, seroconversion should be assessed before travel. In case of incomplete vaccination or failure of vaccine, pooled immunoglobulins are recommended before travel.¹⁶³ They are 85% to 90% effective for protecting against HAV infection.

Hepatitis E Virus

Background and Epidemiology

HEV, a positive-stranded RNA virus belonging to the family *Herpesviridae*, primarily spreads via the fecal-oral route. The incubation period is estimated to be around 2 to 6 wk.¹⁶⁴ Anicteric hepatitis is more common than clinically overt disease and is seemingly more frequent in adults than in children.¹⁶⁴ HEV is highly endemic in SA countries. In India, HEV infection is responsible for 30% to 70% of cases of acute sporadic hepatitis and is a major cause of ALF.^{164,165} In Pakistan, up to 20% to 22% of adults and 2.4% of children were found to have acute hepatitis because of HEV.¹⁶¹ In Nepal, HEV accounts for 15% to 50% of acute hepatitis cases.¹⁶⁶ HEV is the leading cause of acute hepatitis and ALF in Bangladesh.¹⁶⁷ In a recent meta-analysis of SOTRs, the seroprevalence of HEV infection was 20%, with the highest prevalence of 27% in liver transplant recipients and the lowest in lung transplant recipients.¹⁶⁸ HEV in liver transplant recipients has been associated with an increased risk of graft failure and high chances of chronicity.¹⁶⁸⁻¹⁷⁰ There are few reports of liver transplantation in HEV infection. In a report from India, 9 patients with ALF because of HEV infection underwent liver transplantation and none of them developed any posttransplant recurrence because genotype 1 is predominantly seen in the Indian population, which is not usually chronic.¹⁷¹

Screening of Donors and Candidates

All transplant recipients should undergo serology for HEV (IgM anti-HEV).⁵ If a liver transplant candidate

is positive for IgM HEV, then they can proceed for liver transplantation; however, non-liver candidates should wait for complete recovery before being accepted for transplantation.

There are no reports of the donor-to-recipient transmission of HEV in organ transplantation, so donors are not screened before transplantation for HEV. However, transfusion-transmitted HEV infections have been reported, so transmission via organs seems possible.^{165,170} Donors with acute infection are not accepted; however, those with remote infections (eg, HEV IgG positive) can be accepted as donors.⁶

Treatment

Treatment is largely supportive, with consideration of the reduction of immunosuppression.¹⁷⁰ A study by Kamar et al¹⁷² showed that the addition of ribavirin along with a reduction in immunosuppression was effective in sustained virological response in the majority of SOTRs with HEV infection.

Prevention for Recipients Living in or Traveling to Endemic Areas

Immunocompromised travelers to HEV endemic regions should take care of safe food handling, good handwashing practices, and water precautions (Table 4).^{46,53} Travelers should not eat food from street vendors. There is no commercially available vaccine for HEV.

Hepatitis C Virus

Background and Epidemiology

HCV causes both acute and chronic infection; however, unlike HBV, HCV has a higher propensity to lead to chronic viremia, and 25% of these patients can develop chronic hepatitis.^{173,174} HCV in SA is primarily spread from infected needles, blood transfusion, dental and surgical procedures, and unsafe tattoo practices.^{161,174}

In India, the estimated prevalence of HCV is about 0.5% to 1.5%.¹⁷⁴ Despite low prevalence, India accounts for a significant proportion of the global HCV burden because of its large population of 1.3 billion. Approximately 12 to 18 million people are thought to be infected with HCV in the country.¹⁷⁴ Pakistan has a 4% to 5% prevalence of HCV.¹⁶¹ In Bangladesh and Nepal, the prevalence of HCV is <1%.^{166,167} HCV infection is a common cause of liver failure. The long-term patient and graft outcome of HCV-positive patients undergoing liver or non-liver organ transplantation is inferior to those who are HCV negative.^{175,176} Nowadays, the prognosis is much better because of the availability of direct-acting agents for the treatment of HCV before and after transplantation.^{177,178}

Screening of Donors and Acceptance Criteria

HCV antibody screening is mandatory for all donors.⁵ For living donor SOTRs except for liver, if testing for HCV antibody is negative, then nuclear acid test (NAT) is not recommended. In deceased donor transplants, HCV NAT should be done because the infection might be in the window period, and HCV antibody and seroconversion take more than a month.^{5,6} Anti-HCV antibody positivity implies either a treated infection or active infection or a false-positive result, in which case a quantitative NAT

is performed; and if the HCV NAT is negative, then the donor can be accepted.^{6,179} For liver transplants, NAT is performed on all donors.

Donor-to-recipient transmission of HCV has been reported in organ transplantation. Transplantation of HCV-positive organs to HCV-positive recipients is practiced in both living and deceased donor transplant programs because of the availability of very effective directly acting antiviral drugs.¹⁷⁹⁻¹⁸¹ There are now many reports of transplantation of organs from HCV-positive donors to HCV-negative recipients and treatment of these recipients thereafter.^{181,182} Teams considering this must have a post-transplant treatment plan in place.

Candidate Screening and Acceptance

All transplant candidates should undergo serology for HCV (anti-HCV antibody) and HCV RNA qualitative PCR.⁵ With the availability of very effective directly acting antiviral agents, HCV can be treated pre- or posttransplantation. The treatment can be initiated in the pretransplant period and continued posttransplant or can be initiated posttransplant for a duration of 3 mo.^{178,179}

Prevention of Recipients Living in or Traveling to Endemic Areas

There is no vaccine for HCV; hence, prevention depends on education and avoidance of high-risk exposures. SOTRs and travelers should be counseled to avoid contact with nonsterile needles, syringes, cosmetic and tattoo procedures, or other risky behavior.^{46,52} In case of exposure, HCV RNA testing should be done after 2 to 6 wk.

Hepatitis B Virus

Background and Epidemiology

Risk factors for HBV infection include exposure to infected blood products and body fluids, neonatal exposure, medical equipment, body piercing, sexual activity, dental treatment, cosmetic procedures, tattoos, acupuncture, and sharing of personal grooming items.¹⁸³ HBV infection is still common in SA, because vaccination is not universal and is mostly limited to high-risk cases and children.¹⁸⁴ Recent estimates show that India and Nepal have a low prevalence (nearly 2%) of HBV infection, whereas Pakistan and Bangladesh have intermediate endemicity (nearly 4%) of HBV infection.^{161,166,167,174} HBV infection is the most common cause of cirrhosis in SA countries, with approximately one-third of mortality caused by chronic liver disease because of hepatitis B.¹⁸⁴ The recurrence of HBV after transplantation is going down with the availability of antiviral drugs.¹⁸⁵

Screening of Donors and Acceptance Criteria

All potential donors should be screened for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc; both IgM and IgG anti-HBc).^{5,7} Donors who are HBsAg negative and anti-HBc positive might be those who recovered from HBV infection, chronic carriers (occult hepatitis B with detectable HBV DNA), or false positive. In these donors, quantitative HBV nucleic acid testing by PCR should be done.^{5,7} Donors with HBsAg and IgM anti-HBc positivity have acute hepatitis and are excluded from donation. Donors who are HBsAg negative

and IgM anti-HBc positive might be in the window period and the donation should be avoided.⁵ In HBsAg negative and IgG anti-HBc positive donors, HBV NAT by PCR should be done and if it is negative, then organs can be used in recipients who are fully vaccinated with protective hepatitis B surface antibody (anti-HBs-Ab) titers of >100 IU/mL or who were previously infected with HBV.¹⁸⁶⁻¹⁸⁸ In the case of non-liver grafts, the chances of de novo HBV infection from IgG anti-HBc positive donors are low, and these donors can be accepted with plans for posttransplant monitoring or prophylaxis.^{186,187} Transplantation of HBsAg or DNA-positive organs to HBV-positive recipients are used in some deceased donor transplants; however, this is not widely accepted in living donor transplant programs.¹⁸⁷⁻¹⁸⁹ HBsAg-positive liver donors should be accepted for HBsAg negative recipients only in exceptional circumstances and with full informed consent as well as plans for long-term (often lifetime) antiviral treatment.¹⁸⁹

Candidate Screening

In kidney and other SOT transplant candidates, HBsAg and core antibody testing are sufficient (IgG and IgM) for hepatitis B screening; however, for liver transplant candidates, HBV DNA PCR is also done routinely.^{5,7} Testing for HBV surface antibody allows for vaccination of those who are seronegative. Recipients of HBsAg-positive organs should be treated with long-term antivirals for HBV to prevent HBV reactivation.¹⁸⁹

Prevention and Prophylaxis

The preventive strategies for HBV infection should include a vigilant screening of blood and blood products and routine testing of tissue and organ donors for HBsAg. Vaccination for HBV and testing for anti-HBs should be performed in all transplant candidates, and if titers are inadequate, these patients should be revaccinated or booster doses should be given, because a serological response is poor posttransplant.⁵ When feasible, serologic testing of anti-HBs antibody 1 mo after completion of the vaccine series should be performed to confirm immunity. Revaccination with a higher-dose HBV vaccine should be considered if the antibody response is suboptimal (anti-HBs <10 mIU/mL).⁵

Recipients Living in or Traveling to SA

All SOTRs should be fully vaccinated with adequate antibody titers (>10 IU/mL). If titers are low, a booster dose should be given before traveling. Precautions should be taken to reduce exposure to infected body fluids, blood products, and unprotected new sex contacts.⁴⁶

Hepatitis D Virus

Background and Epidemiology

Hepatitis D virus (HDV) is a dependent virus and relies on HBV to synthesize the pathogenic genomes. HDV is acquired either as a coinfection with HBV or as a superinfection in chronic HBV-infected patients.¹⁹⁰ Chronic HDV infection results in liver damage and can lead to the rapid development of end-stage liver disease. The prevalence of HDV is declining and currently, it is very low in India and SA. In 1 recent study, none of the patients infected with HBV was found to have hepatitis D¹⁹¹; however, in

Pakistan, a survey revealed the prevalence of hepatitis D in 16.6% of patients who were HBV positive and in 50% to 60% of those attending the clinics.¹⁹²

Diagnosis

HDV IgM anti-HBc, and IgM anti-HDV are markers of acute viral infection, whereas anti-HDV IgG is positive in chronic HDV infection. HDV DNA is transiently positive in acute HDV infection, and it is persistently positive in high titers in patients with chronic HDV.^{190,191}

Donor and Recipient Screening

Screening is recommended in HBV DNA or surface antigen-positive patients because HDV can lead to end-stage liver disease in chronic HBV-positive patients after coinfection or superinfection with HBV.^{190,192}

DIARRHEA INCLUDING TRAVELER'S DIARRHEA

Background

Diarrhea, especially infective diarrhea, is common in SA. In addition to immunosuppressed status, poor hygiene, malnutrition, and inadequate resources contribute to the high incidence of diarrhea in this region. In addition to common causes of acute diarrhea caused by viral, bacterial, and helminthic infections, opportunistic infections with organisms such as *Cryptosporidium*, *Strongyloides*, *Cystoisospora belli*, *Cyclospora spp.*, *Microsporidia*, and norovirus are the causative agents of diarrhea in SOTRs.¹⁹³

Traveler's Diarrhea

SA carries a high risk of traveler's diarrhea in transplant recipients, with an incidence of 10% to 40%.^{193,194} The risk is highest during the first 14 d of travel.^{193,195} The most common causes of traveler's diarrhea include *Enterotoxigenic E coli* followed by *Enteroaggregative E coli*, *Shigella*, *Salmonella*, and *Campylobacter jejuni*.¹⁹⁴ Additionally, traveler's diarrhea can occur because of other parasitic and helminthic infections in SA like *Cryptosporidium*, *Cyclospora*, *Giardia*, *Ascaris*, and helminths.^{193,194} Amebiasis is common and should always be included in the differential diagnosis of traveler's diarrhea. Mycophenolate mofetil can sometimes cause chronic diarrhea, occasionally triggered by an infection.

Clinical Features and Diagnosis

Traveler's diarrhea is characterized by an increase in the frequency of bowel movements and a change in the consistency of the stool (soft to liquid) that usually begins within 2 to 3 d of arrival. The symptoms might range from acute watery diarrhea to bloody diarrhea to chronic diarrhea. Patients can have nausea, vomiting, abdominal pain, cramps, or fever.¹⁹⁴ Acute watery diarrhea is usually caused by bacterial or viral infections, whereas chronic diarrhea is usually caused by parasitic infections like *Giardia*, *Amebiasis*, or opportunistic pathogens like *microsporidia* or *cryptosporidium*.^{193,194} Brief episodes with resolution do not usually require further evaluation. If symptoms persist, then stool microscopy, stool culture, and special stains should be done to look for opportunistic pathogens.¹⁹⁴⁻¹⁹⁶ Multiplex PCR is becoming increasingly available but it is very sensitive and sometimes detects bystander organisms.

Few patients might need colonoscopy with biopsy for diagnosis. Cytomegalovirus PCR in blood should be done as a part of the evaluation of chronic diarrhea in SOTRs.¹⁹⁵

Management

Most episodes are mild and need fluid replacement and supportive treatment. Intravenous rehydration may be needed in severe diseases.¹⁹⁶ A decrease in the gut metabolism of tacrolimus can lead to elevated circulating levels and may result in toxicity.¹⁹⁶ The empirical treatment for diarrhea in SA should include a combination of ciprofloxacin plus tinidazole (500 mg of each) twice daily for 3 to 5 d if symptoms are moderate to severe (≥ 3 stools/d and all patients with bloody diarrhea or fever), which should cover most pathogens in this region including *Amoeba*, *Giardia*, and bacterial dysentery. The alternative antibacterial is azithromycin 500 mg once daily for 3 d.¹⁹⁶ Bacterial resistance to antibiotics, especially fluoroquinolones, is common in SA countries, and if symptoms persist, then further treatment should be based on microbiological investigations.

Recipients Traveling to Endemic Areas

Travelers should be instructed to focus on personal hygiene as well as strict food and water precautions. Measures like regular handwashing, use of sanitizers, and proper washing of raw food materials play an important role. Travelers should be advised to avoid foodstuff that has not been freshly prepared or properly cooked. Salads, reheated or uncovered foods, and any food cooked in unhygienic circumstances should not be consumed.^{52,196} (Table 4). Bottled water from a reputed company with an intact seal should be used for drinking. Travelers should avoid walking barefoot because of the risk of strongyloidiasis.

VACCINATIONS AND SOTs IN SOUTH ASIA

Patients should be screened for vaccination history and should ideally be immunized early in the course of their disease, when vaccines are most likely to be effective, or during pretransplant evaluation.^{197,198} Posttransplant immunosuppressive drugs impair vaccine immune responses resulting in decreased efficacy and duration of vaccine-induced protection.¹⁹⁷ Serologic testing for vaccine-preventable diseases like hepatitis A and B should also be performed to help guide vaccine planning. Certain infections are more common in the SA region, so vaccination for prospective transplant recipients and those traveling to these regions should be advised.^{109,199} Recommendations for vaccination in South Asia for transplant candidates and recipients are given in Table 5. Recommendations for travelers to SA are provided in Table 6.

CONCLUSIONS

The SA region is a hotbed for infections. SOTRs are at higher risk of all types of infections including the usual as well as opportunistic infections. The morbidity and mortality because of infections are high in this region and infections are among the most common causes of graft failure and death in this region. Adequate screening of transplant candidates and donors is of paramount importance

to detect any infection and treat them before proceeding with transplantation. South Asia is endemic to TB, making adequate pretransplant assessment critical. Because food, water, and mosquito-borne diseases are common in this region and cause many bacterial, parasitic, and viral infections, adequate preventive measures and good hygiene should be maintained by SOTRs living in these regions as well as travelers visiting this region. Certain infections like histoplasmosis, sporotrichosis, talaromycosis, leishmaniasis, melioidosis, and Japanese encephalitis are common in some areas of SA, so screening and prophylaxis for recipients and travelers can be restricted to that area. Transplant candidates should be fully vaccinated before transplant because seroconversion is poor after transplant. Transplant travelers to these areas should take prophylaxis for malaria, recommended vaccines, and other precautions before visiting endemic regions in SA.

FUTURE RESEARCH

Although the SA region has a high incidence of endemic and nonendemic and opportunistic infections, the literature in SOTRs is still scarce. Many recommendations are extrapolated from local case series and guidelines from high-income regions. There is a significant need for more research in SOTRs on the diseases that are prevalent in this region like TB, malaria, arboviral diseases, posttransplant diarrhea, endemic fungal infections, and others. TB serves as an excellent example of how outside guidelines do not fit well with local practices. Multicenter prospective studies should be conducted through the collaboration of large public and private sector hospitals to generate further data on best practices for screening, prophylaxis and treatment, enhancing the safety, and best outcomes for transplant recipients in this region.

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