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


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. (Transplantation 2023;107: 1910–1934).

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),...
...and pancreas (25). 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, Kirgizistan).

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. 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, toxocariasis, leptospirosis, and amebiasis, also represent a significant burden.

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).

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. 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, Madanta-Medicity, Gurgaon, Madras Medical College Chennai, along with many others) along with leading experts from...
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
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. 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. TB is 20 to 74 times as frequent and carries a high mortality in SOTRs. The reported incidence of TB in SOTRs in SA is 5.7% to 12.3%. 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>
<thead>
<tr>
<th>Table 2</th>
<th>Routine screening for potential SOT donors and recipients in South Asia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test</strong></td>
<td><strong>Candidate</strong></td>
</tr>
<tr>
<td>HIV</td>
<td>Yes</td>
</tr>
<tr>
<td>Fourth-generation Ag/Ab screen</td>
<td>Yes</td>
</tr>
<tr>
<td>NAT</td>
<td>No</td>
</tr>
<tr>
<td>CMV IgG antibody</td>
<td>Yes</td>
</tr>
<tr>
<td>EBV IgG</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Yes</td>
</tr>
<tr>
<td>Anti-Hbc Ab</td>
<td>Yes</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>If liver transplant</td>
</tr>
<tr>
<td>Anti-Hbs Ab</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td></td>
</tr>
<tr>
<td>Antibody testing</td>
<td>Yes</td>
</tr>
<tr>
<td>NAT</td>
<td>Yes</td>
</tr>
<tr>
<td>Strongyloides IgG</td>
<td>Yes</td>
</tr>
<tr>
<td>Toxoplasma IgG (heart transplant)</td>
<td>Yes</td>
</tr>
<tr>
<td>Syphilis screening by enzyme immunoassay (TP-EIA) (with additional testing if positive)</td>
<td>Yes</td>
</tr>
<tr>
<td>Mycobacterium TB</td>
<td>History of close contact or past history of inadequately treated TB</td>
</tr>
<tr>
<td>TST or IGRA</td>
<td>Yes</td>
</tr>
<tr>
<td>Urine culture</td>
<td>Yes</td>
</tr>
<tr>
<td>Blood culture</td>
<td>If indicated clinically</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Infection</th>
<th><strong>Test</strong></th>
<th><strong>Screening in Candidate</strong></th>
<th><strong>Deceased donor</strong></th>
<th><strong>Living donor</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>TST or IGRA</td>
<td>History of contact or past history of inadequately treated TB</td>
<td>NA</td>
<td>History of contact or past history of inadequately treated TB</td>
</tr>
<tr>
<td>Melioidosis (regional)</td>
<td>Culture</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Histoplasma</td>
<td>Antigen Urine</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Penicillium marneffei</td>
<td>Culture</td>
<td>Yes, if clinical disease suspected</td>
<td>Defer donor</td>
<td>Yes, if clinical disease suspected</td>
</tr>
<tr>
<td>Sporothrix (regional)</td>
<td>Culture</td>
<td>Yes, if clinical disease suspected</td>
<td>Defer donor</td>
<td>Yes, if clinical disease suspected</td>
</tr>
<tr>
<td>Malaria</td>
<td>Smear and antigen test</td>
<td>Yes, if clinical disease suspected</td>
<td>Yes</td>
<td>Yes, if clinical disease suspected</td>
</tr>
<tr>
<td>Leishmania (Bihar, Nepal)</td>
<td>Leishmania antigen/antibody</td>
<td>Yes, if clinical disease suspected</td>
<td>Yes</td>
<td>Yes, if clinical disease suspected</td>
</tr>
<tr>
<td>Strongyloides</td>
<td>Strongyloides IgG</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, if elevated LFTs</td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>IgM HEV</td>
<td>Yes</td>
<td>If elevated LFTs</td>
<td>Yes, if elevated LFTs</td>
</tr>
<tr>
<td>Rabies</td>
<td>IgM</td>
<td>No</td>
<td>Yes, if unknown encephalitis</td>
<td>In peak season</td>
</tr>
<tr>
<td>Dengue</td>
<td>NS1 antigen/IgM</td>
<td>In peak season</td>
<td>Yes</td>
<td>In peak season</td>
</tr>
<tr>
<td>Leptospirosa</td>
<td>IgM</td>
<td>Yes, if clinical disease suspected</td>
<td>Yes</td>
<td>Yes, if clinical disease suspected</td>
</tr>
<tr>
<td>Filariae (North India)</td>
<td>Filarial antigen or microfilariae in blood</td>
<td>Yes, if clinical disease suspected</td>
<td>Yes, if suspected</td>
<td>Yes, if clinical disease suspected</td>
</tr>
</tbody>
</table>

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

*intravenous 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.
seen in about 5% of patients. 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.

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 (spumt examination, bronchoalveolar lavage [BAL], needle aspiration, or biopsy).

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 deactivation for evidence of TB in either the graft or elsewhere.

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>
<thead>
<tr>
<th>Infection</th>
<th>Advice to travelers visiting endemic region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>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.</td>
</tr>
<tr>
<td>Typhoid fever</td>
<td>Drink bottled water from a reliable source, frequently wash hands, and get vaccinated before travel to endemic area.</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>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.</td>
</tr>
<tr>
<td>Melioidosis</td>
<td>Avoid exposure to soil and rainy water and avoid traveling to endemic regions during natural calamities like tsunami and floods.</td>
</tr>
<tr>
<td>Scrub Typhus</td>
<td>Protect against bite of the vector (mite) and minimize outdoor activities when visiting the endemic areas.</td>
</tr>
<tr>
<td>Mucormycosis</td>
<td>Avoid areas with heavy construction and moist surroundings. Air filter/AC should be regularly cleaned to prevent colonization with Mucor species.</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>Avoid going to construction areas, being exposed to caves, and working on poultry farms.</td>
</tr>
<tr>
<td>Talanaroscopy</td>
<td>Avoid highlands in endemic areas especially during the rainy season.</td>
</tr>
<tr>
<td>Sporotrichosis</td>
<td>Avoid skin-penetrating trauma or contact with cats and wear appropriate gloves during gardening activities.</td>
</tr>
<tr>
<td>Arboviruses: chikungunya, dengue, and Zika virus</td>
<td>Reduce skin exposure to mosquito bites with barrier methods, such as insect repellents and long-sleeved or permethrin-treated clothing, coils, and vaporizers.</td>
</tr>
<tr>
<td>Malaria</td>
<td>Chemoprophylaxis against malaria should be taken.</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Travelers spending extensive time in Japanese encephalitis endemic areas are recommended to get vaccinated before travel.</td>
</tr>
<tr>
<td>Rabies</td>
<td>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.</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Avoid undercooked meat and unwashed fruits and vegetables, which may possibly be contaminated with oocysts of Toxoplasma.</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>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.</td>
</tr>
<tr>
<td>Travelers diarrhea and strongyloides</td>
<td>Any uncooked food, poorly cooked food, or food that is not fresh should not be eaten.</td>
</tr>
<tr>
<td>HAV and HEV</td>
<td>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.</td>
</tr>
</tbody>
</table>

AC, air conditioning; DEET, diethyl toluamide; HAV, hepatitis A virus; HEV, hepatitis E virus; SOT, solid organ transplantation; TB, tuberculosis.
may provide information about their TB status. Deceased donors with known or suspected active TB should not be accepted.\textsuperscript{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

| 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 | | |
| Herpes Zoster | One booster 10 y | Booster every 10 y | |
| Live vaccine (Zostavax Inactivated (RZV- Shingrix) | 2 doses 4 wk apart | Contraindicated | |
| Hepatitis A          | 2 doses, 6 mo apart | Booster dose if antibody titer <10 mU/mL | |
| Inactivated          | at least 8 wk before transplant | | |
| Hepatitis B          | 3–4 doses before transplant, double dose in those with CKD and dialysis | Booster dose if antibody titer <10 mU/mL | |
| Inactivated          | Should be completed after transplant if not fully vaccinated | | |
| Human papilloma virus | 3 doses at 0, 1, 6 mo | Should be completed after transplant if not fully vaccinated | |
| Inactivated          | Single dose at least 4 wk before transplant | | |
| Inactivated          | 1 dose annually | | |
| Live Measles, Mumps, Rubella | Should be completed 4 wk before transplant | Contraindicated | Contraindicated after transplant |
| Live vaccine Meningococcal | 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 |
| Inactivated Pneumococcal | 1 dose PCV-13, followed after 8 wk by 1 dose PPV23 | Booster dose PPV23 after 5 y | |
| Inactivated—conjugated polysaccharide | Polysaccharide: 1 dose or conjugated: 1 dose | Polysaccharide: needs booster 3 y | |
| Typhoid Inactivated | Pretransplant 2 doses 1 mo apart | Booster not required | |
| Varicella Live vaccine | | | |

\textsuperscript{a}Efficacy 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 | Complete before travel, consider documenting seroconversion |
| Typhoid vaccine/inactivated | Polysaccharide–Conjugated: 1 dose | Can give immunoglobulin for prevention |
| Rabies/inactivated | Preexposure - 3 doses at d 0, 7, and 21 or 28 d | Needs booster every 2 y |
| Japanese encephalitis/inactivated-live | 2 doses 4 wk apart | Booster not required |
| Dengue/live | Contraindicated | Often given for higher-risk travel |

SOT, solid organ transplantation.
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.\textsuperscript{16} Lungs from donors with significant residual damage from prior TB should not be used for donation.\textsuperscript{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.\textsuperscript{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 this region. The sensitivity and specificity of these tests are poor in our setting.\textsuperscript{19} The Revised National TB Control Program of India does not recommend universal screening for LTBI in the general population.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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/clarithromycin 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.\textsuperscript{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.\textsuperscript{19,23,24} Regarding IGRA, 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.\textsuperscript{23}

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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. 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. Early use of sensitive radiological investigations (e.g., CT scan) and invasive procedures to obtain specimens for microbiological or histological tests is critical in making a diagnosis. 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 fluoroquinolones. 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%. 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. 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 rifampicin (RIF; rifabutin) and the doses should be adjusted accordingly. Using rifampicin 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 rifampicin-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 IGRA 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. In India, the incidence is reported to be as high as 235 to 976/100,000 persons per year. 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. 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. If left untreated, the patient may develop intestinal bleeding and ileocecal perforation in the third week of symptoms leading to peritonitis and septicaemia. Some patients might develop neurological manifestations like altered sleep patterns, acute psychosis, meningitis, and encephalopathy. In a series of 3 cases of Salmonella in renal transplant recipients, the disease course was more serious than in nonimmune-compromised patients.

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. Widal test or Typhi dot immunoglobulin (Ig) M have poor sensitivity and specificity, so they are not recommended.

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. In the surveillance of enteric fever in the Asia project study, MDR strains (i.e., 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. 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. 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. 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, Typhbar-TCV has recently been prequalified for use in several countries and can be given after transplant. 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 vaccine (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.

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. The peak occurs in summer and epidemics after monsoons and heavy rainfall. Humans acquire infection by penetration of the spirochete via abraded skin or mucous membrane. 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. Myalgia, conjunctival suffusion, jaundice, hemorrhage, and acute kidney injury are common symptoms. There are reports of liver transplantation because of liver failure by leptospirosis. 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. Polymerase chain reaction (PCR) is more specific but not widely available in the region. 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.

Donor and Recipient Screening and Donor’s Acceptance Criteria
Routine Donor Screening in Asymptomatic Donors or Candidates Is not Recommended
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
Travelers to SA
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.

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. In India, the majority of cases are reported from of Karnataka and Tamil Nadu. 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.

Few cases of melioidosis following organ transplantation have been reported and most of them are from India. 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. Other manifestations include visceral abscesses involving the liver, spleen, kidney and prostate, septic arthritis, osteomyelitis, and intramedullary abscess are also seen. 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.

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, 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.

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. 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. Scrub typhus has been reported widely in India and Pakistan and is a major cause of pyrexia of unknown origin. Risk factors include living in rural areas, sleeping outdoors, and recent rainfall, conditions that increase the risk of mite bites. 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.

Clinical Features and Diagnosis

Manifestations include isolated fever, maculopapular rash (eschar), lymphadenopathy, liver dysfunction, pneumonia, meningitis/meningoencephalitis, acute kidney injury, and septic shock. 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. Diagnosis requires the demonstration of IgM antibodies or nucleic acid testing by PCR.

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.

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.

ENDEMIC FUNGAL INFECTIONS

Mucormycosis

Background and Epidemiology

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

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.

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. Corticosteroid doses should be kept as low as possible. Air filters and conditioners should be regularly cleaned to prevent colonization with Mucorales species. Posaconazole or other antifungals active against Mucorales would routinely be used for recipients of donor lungs that are colonized with Mucorales species on pre- or postransplant respiratory culture and may be considered in organ recipients requiring very high levels of immunosuppression.

Management

Wide surgical excision or debridement, reversal of underlying risk factors, along with antifungal treatment
is the mainstay of treatment. Liposomal amphotericin B should be used as induction therapy followed by Posaconazole or similar as maintenance therapy. The duration of treatment for invasive mucormycosis is based on clinical and radiological resolution.

Selected Reading: 5, 8, 75-76

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

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.

Clinical Features and Diagnosis
The presentation is nonspecific with fever, lymphadenopathy, and nodules/infiltrate on chest imaging and can mimic TB. Diagnosis requires demonstration of the fungus in blood, fluid, or tissue specimens obtained by bronchoscopy or FNAC/biopsy. In patients with disseminated infection, blood cultures using a lysis centrifugation system can help in early diagnosis. Serology is not very useful for diagnosis in immunocompromised patients. Awareness of the possibility of histoplasmosis is necessary when investigating a post-transplant 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. Donors with active histoplasmosis are excluded from donating organs. 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.

Recipient Screening and Posttransplant Monitoring
Pretransplant screening for histoplasmosis is of limited value. 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.

Prevention and Prophylaxis, Including for Recipients Traveling to Endemic Areas
Because histoplasmosis is acquired from the environment, post-transplant 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.

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 post-transplant histoplasmosis is 12 mo, guided by clinical and radiographic responses.

Talaromycosis

Background and Epidemiology
Talaromyces marneffei (formerly penicilliosis) is caused by a dimorphic fungus Talaromyces marneffei, endemic in Southeast Asia and Northeast India. Human infection occurs via inhalation of T. marneffei spores found in infected soil, often associated with bamboo rats. 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. The disease increases in rainy seasons and is associated with high mortality in organ transplant recipients.

Clinical Features and Diagnosis
Manifestations are similar to histoplasmosis and TB, for example, fever, weight loss, cough, anemia, lymphadenopathy, and hepatosplenomegaly. Skin lesions are seen only in 30% to 60% of patients, and biopsy can help with diagnosis. 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.

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

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.
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. 86,76 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. 30 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

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 head ache, 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.

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.6,97 Transmission is through mosquito bites (Culex) through a zoocentric 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 sometimes.101 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.107 Demonstration of virus antigen through fluorescent antibody testing in brain biopsy
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 antirabies 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.3,7,8

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 posttransplant 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.

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. Patients can have cerebral abscesses, encephalitis, myocarditis, pneumonitis, chorioretinitis, multiorgan involvement, and disseminated disease. 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. The late seroconversion among transplant recipients limits the diagnostic accuracy of IgM for the diagnosis of acute toxoplasmosis in this population.

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. 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 jirovecii) is effective. Alternatives include a combination of clindamycin, pyrimethamine, and leucovorin; atovaquone; or dapsone plus pyrimethamine. The duration of prophylaxis is not well defined but should be given for at least 3 mo posttransplant. 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. 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.

Management of Active Infection
Treatment of active disease includes pyrimethamine, sulfadiazine, and folic 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. 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.

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. 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. VL (also known as the kala-azar disease) is caused by Leishmania infantum, Leishmania infantum chagasi, and Leishmania donovani complexes.

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. VL is the predominant form in SOTRs, most frequently in kidney recipients. 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.

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. VL presents as fever, weight loss, hepatosplenomegaly, and pancytopenia. Atypical presentations can also be seen. 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.

Demonstration of L. donovani bodies in the bone marrow and splenic aspirate remains the gold standard for diagnosis. 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. 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. 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. Routine testing of donors and transplant candidates is not recommended. 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). 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. Conventional amphotericin B deoxycholate is also effective but carries greater toxicity.

122,123 Patients can have cerebral abscesses, encephalitis, myocarditis, pneumonitis, chorioretinitis, multiorgan involvement, and disseminated disease. 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. The late seroconversion among transplant recipients limits the diagnostic accuracy of IgM for the diagnosis of acute toxoplasmosis in this population. 124

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67 Malignancy (e.g., Kaposi sarcoma) is a contraindication to transplantation. 128,130 Immunosuppressed patients have higher chances of clinical disease and severe disease compared with immunocompetent individuals or donors who are mostly asymptomatic without visceromegaly or cytopenias.

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Management of Active Infection
Treatment of active disease includes pyrimethamine, sulfadiazine, and folic 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. 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.

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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.134,140 Obtaining evidence of cure by PCR 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

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 tachycardia may lead to acute kidney injury.134,135 The extraintestinal atypical manifestations may present as respiratory tract disease, pancreatitis, and cholangitis.134,138

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

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 with corticosteroids. The 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.146 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

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

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. SOTRs should receive the HAV vaccine series before traveling to moderate- to high-risk infection areas. Ideally, seroconversion should be assessed before travel. In case of incomplete vaccination or failure of vaccine, pooled immunoglobulins are recommended before travel. 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. Anicteric hepatitis is more common than clinically overt disease and is seemingly more frequent in adults than in children. 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. In Pakistan, up to 20% to 22% of adults and 2.4% of children were found to have acute hepatitis because of HEV. In Nepal, HEV accounts for 15% to 50% of acute hepatitis cases. HEV is the leading cause of acute hepatitis and ALF in Bangladesh. 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. HEV in liver transplant recipients has been associated with an increased risk of graft failure and high chances of chronicity. 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.

Screening of Donors and Candidates

All transplant recipients should undergo serology for HEV (IgM anti-HEV). 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. Donors with acute infection are not accepted; however, those with remote infections (eg, HEV IgG positive) can be accepted as donors.

Treatment

Treatment is largely supportive, with consideration of the reduction of immunosuppression. A study by Kamar et al 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. 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. HCV in SA is primarily spread from infected needles, blood transfusion, dental and surgical procedures, and unsafe tattoo practices. In India, the estimated prevalence of HCV is about 0.5% to 1.5%. 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. Pakistan has a 4% to 5% prevalence of HCV. In Bangladesh and Nepal, the prevalence of HCV is <1%. 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. Nowadays, the prognosis is much better because of the availability of direct-acting agents for the treatment of HCV before and after transplantation.

Screening of Donors and Acceptance Criteria

HCV antibody screening is mandatory for all donors. 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. 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.\(^7\) 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.\(^{6,52}\) 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.\(^{185}\) 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.\(^{188}\)

#### 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 are considered if the antibody response is suboptimal (anti-Hbs <10 mIU/mL).\(^5\) 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 D.\(^{191}\)
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 Enterogaugreggative 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.193,195 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 the frequency of bowel movements and a change in the fluid content to bloody diarrhea to chronic diarrhea, occasionally triggered by an infection.193,194 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 or cryptosporidium. 193,194 Brief episodes with resolution or cryptosporidium.193,194 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, 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.192 (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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REFERENCES


6. Clemente WT, Pierrotti LC, Abdala E, et al. Recommendations for management of endemic diseases and travel medicine in solid-organ


