Recipient Screening Prior to Solid-Organ Transplantation

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Screening a potential transplant recipient for infectious diseases is an important component of the transplantation process. Such screening may lead to the discovery and treatment of occult active infection, may help determine posttransplant prophylactic strategies, or may disqualify the recipient from receiving a transplant. The pretransplant period also affords an opportunity for updating vaccination status and providing education regarding the reduction of posttransplant infectious risks. The present brief review will outline the investigation of preexisting active infection, as well as latent bacterial, mycobacterial, fungal, parasitic, and viral infections. Recommendations for pretransplant immunization and education are provided.

The topics of donor and recipient infectious disease screening and pretransplant interventions recently have been reviewed in detail elsewhere [1–3]. The Immunocompromised Host Society has published guidelines on pretransplant interventions [4] and donor and recipient screening [3]. The Infectious Disease Committee of the American Society for Transplantation (AST) is currently writing guidelines for the prevention and management of infections in transplant recipients, including guidelines for pretransplant evaluation. The AST and American Society of Transplant Surgeons (ASTS) have also published clinical practice guidelines for evaluation of renal transplant candidates in general [5].

The relationship between pretransplant exposure to infections and posttransplant risk is complex [1–7]. Although certain screening tests, such as serological testing for HIV, cytomegalovirus (CMV), hepatitis B virus (HBV), and hepatitis C virus (HCV), are obtained by virtually all transplant centers, there is considerable center-to-center variation in how this information is used to make transplantation-related decisions.

Preexisting Active Infection

Potential transplant candidates with end-stage organ disease are subject to a variety of infections, which vary depending on the organ that is failing [4, 6]. Renal transplant candidates may have infections related to hemodialysis access or peritoneal dialysis catheters. Complicated upper-tract urinary infections may also occur. Liver transplant candidates are susceptible to spontaneous bacterial peritonitis and aspiration pneumonia because of altered mental status. Lung transplant candidates are subject to pneumonias, sometimes with multiresistant organisms, especially in those with cystic fibrosis. Heart transplant candidates may have pneumonias or infections related to intravascular devices. All of the above may be localized or generalized, with or without manifestations of sepsis, and occasionally may be indolent or occult. For any organ transplant candidate, bacteremia and candidemia before transplantation are of particular importance and must be fully and effectively treated to avoid not only posttransplant sepsis but also the formation of mycotic aneurysms at anastomotic suture lines.

In general, preexisting active infection should be fully treated whenever possible. However, there are scant data on which to base a recommendation for the interval between resolution of the infection and transplantation. When possible, cure of the infection should be documented by repeat cultures and radiographic and clinical criteria.

Pretransplant infections related to intravascular devices, such as tunneled central venous catheters, pacemakers, and implantable cardiac defibrillators, should be treated with appropriate...
antibiotics and with device removal. A notable exception is the ventricular-assist device (VAD), which is impractical to remove before heart transplantation. Those patients who are bridged to heart transplantation with a VAD are particularly susceptible to infections related to this large foreign body, which may be in place for $\geq 100$ days. Although frequently starting as drainage at the abdominal drive-line exit site, localized infections can progress to bacteremia or fungemia or abscesses of the VAD pocket [8]. Coagulase-negative staphylococci, Staphylococcus aureus, gram-negative bacilli, enterococci, and yeast can all cause infection in this setting, sometimes sequentially. Because it is prohibitively difficult to remove and replace a VAD prior to transplantation, such infections are often managed with therapeutic courses of intravenous antibiotics and, sometimes, subsequent suppressive antibiotic therapy through the time of transplantation. Fortunately, such infections may be completely cured with vigorous antibiotic therapy before and after transplantation, along with explantation of the device and the recipient’s heart at the time of transplantation [8]. A further course of posttransplant antibiotics directed at the patient’s previous infecting organisms is also prudent.

The AST and ASTS clinical practice guidelines for the evaluation of renal transplant candidates discuss the subject of posttransplant peritonitis in detail [5]. Peritonitis occurs early after transplantation in $\sim 10\%$ of former peritoneal dialysis patients who undergo renal transplantation. Early removal of peritoneal dialysis catheters after transplantation is recommended [5, 9]. These guidelines also state that “it would seem prudent to delay transplantation for a patient with active or recent peritonitis. However, there are no data to suggest what a safe interval between infection and transplantation might be. Documentation of the eradication of infection after the completion of antimicrobial therapy seems appropriate” [5, p. 26].

The above statement regarding the desirability of eradication of active infection could also apply to other types of infections in other organ transplant candidates, including spontaneous bacterial peritonitis or biliary tract infection in liver transplant candidates, pneumonia in lung or heart transplant candidates, and other acute bacterial infections. Where possible, it is desirable to repeat cultures, radiography, or other tests used to diagnose the infection, to document cure. However, as in the case with renal transplant candidates with peritonitis, no definitive recommendation can be made at present as to a particular time interval between infection and transplantation. In my opinion, at least a 2-week delay after resolution of active infection is prudent unless the transplant is considered to be emergent, in which case infection is controlled to the extent possible and antibiotics are continued after transplantation. To some extent, the management is individualized to the particular circumstances of the patient. Consultation with an infectious-disease physician knowledgeable in transplantation infectious disease is helpful.

In some cases, transplantation is done, at least in part, because of infection. Liver transplantation for end-stage liver disease due to HBV or HCV falls into this category, in addition to refractory recurrent cholangitis in the setting of underlying liver disease. In the latter case, the underlying infection is difficult, if not impossible, to eradicate until the recipient organ is removed. In these situations, it is desirable to control and suppress infection to the extent possible prior to transplantation.

Patients who have received pretransplant immunosuppression with steroids or other immunosuppressive medications are subject to an even broader array of opportunistic infections. It is important to detect and fully treat such infections prior to transplantation. Whether receiving exogenous immunosuppression or not, transplant candidates may have current or past histories of fungal or mycobacterial infection (see below). Such infections in active form, such as histoplasmosis, cryptococcosis, tuberculosis (TB), and nontuberculous mycobacteria, constitute a contraindication to transplantation. However, transplantation may be considered once such an infection has been fully treated, with complete resolution of signs, symptoms, and radiographic evidence of disease and with a standard length of therapy for the particular infection involved.

The presence of radiographic evidence of old granulomatous disease, including calcified hilar and mediastinal nodes or splenic calcifications, is not considered to be a contraindication to transplantation, but, as for all patients, skin testing to detect latent TB infection should be done. In those patients who do not have evidence of latent TB infection, particularly in the midwestern United States, such calcifications are often due to past histoplasmosis. A heightened awareness of the possibility of reactivation after transplantation is warranted. In areas where coccidioidomycosis is endemic, screening and secondary azole prophylaxis are likely to be helpful (see below) [10].

**LATENT BACTERIAL INFECTION AND COLONIZATION**

Potential transplant recipients are screened for latent syphilis with a rapid plasma reagin (RPR) assay. If the results are positive, the patient should undergo a specific treponemal test (fluorescent treponemal antibody absorption test or microhemagglutination assay for Treponema pallidum) to determine whether the RPR result is biologically false positive. If the RPR result is low-titer and the patient has received appropriate treatment for syphilis in the past, the patient may be serofast and thus not harboring live treponemes. However, any other positive RPR assay result with positive treponemal test results should be considered an indication of active (presumably latent) syphilis and should be treated according to standard...
guidelines [11]. It is desirable to complete this course of therapy prior to transplantation; however, in emergency situations, management may be individualized.

Vancomycin-resistant enterococcal (VRE) infection and colonization are increasing problems in patients awaiting transplantation. Liver transplant candidates appear to be at particular risk. Posttransplant VRE infection can occur at a variety of sites, most commonly the abdomen but also the bloodstream, urinary tract, and other sites. Gastrointestinal tract colonization and biliary tract colonization are common in liver transplant recipients, and invasive infection is most common in those with surgical complications and multiple operations. In earlier years, reported mortality rates for VRE infection in transplant recipients have been >50%, but the advent of more effective therapy such as linezolid and quinupristin-dalfopristin may improve these outcomes. In addition, mortality in VRE-infected patients also may be attributable to other concomitant medical conditions rather than specifically to VRE [12–14].

Although VRE infection constitutes an increased risk for transplant recipients, no current recommendations have stated that VRE colonization is a contraindication to transplantation. Posttransplant VRE infection may occur in patients without pretransplant colonization, and many colonized patients never develop invasive infection. At present, there is no approved effective agent for VRE decolonization. Some experts recommend pretransplant screening of stool samples for VRE, not for decolonization purposes but rather to identify patients who should undergo isolation and enhanced infection control measures to prevent nosocomial spread (R. Patel and N. Singh, personal communications). Prudent use of vancomycin and other antibiotics, adherence to infection-control guidelines, and a heightened awareness of VRE risk in patients with posttransplant abdominal complications are perhaps the best measures that can be recommended at present.

Methicillin-resistant S. aureus (MRSA) infection also has been found to have a high mortality after transplantation, especially in liver transplant recipients with a deep intra-abdominal focus of infection or bacteremic pneumonia [15]. Pretransplant screening for colonization of the nares and other sites and eradication of colonization with nasal mupirocin ointment, antibacterial washes, and other measures may be attempted, particularly in centers with high rates of MRSA infection [16], but these measures have not completely eradicated this problem (N. Singh, personal communication). As with VRE, screening for MRSA colonization can identify patients who are at higher risk and can lead to more stringent infection-control measures.

Colonization of the airways with bacteria is a common problem in lung transplant candidates. It is common to give a course of antibiotic therapy immediately after transplantation, directed at both the recipient’s and the donor’s colonizing organisms detected by cultures obtained at the time of transplantation. Patients with cystic fibrosis in particular may be colonized prior to transplantation with multiresistant Pseudomonas or Burkholderia species. Burkholderia cepacia is particularly problematic, because infection by this organism has been found to carry an increased morbidity and mortality posttransplant (33% vs. 12% mortality over 6 months in one series) [17]. Many centers do not offer transplantation to Burkholderia-colonized recipients, whereas other centers individualize this decision to the patient’s particular circumstances. Recent research on different levels of risk associated with different Burkholderia genomovars may allow for more precise risk stratification. It appears that genomovar III may be associated with higher risk than the other genomovars [17]. At present, the decision as to whether to perform transplantation for these patients rests with the individual center.

LATENT MYCOBACTERIAL INFECTION

All potential transplant recipients, particularly those from areas where mycobacteria are endemic, should be screened for latent tuberculosis infection with a PPD skin test unless they have a documented previous positive test or previous treated tuberculosis. An anergy panel that includes controls is preferable to an isolated PPD test [5]. Patients with positive PPD test results should be considered for prophylactic therapy with isoniazid, according to standard guidelines [18, 19], after a careful evaluation to exclude active disease that would require combination therapy. If transplantation is urgent or emergent, a patient may be listed prior to completion of prophylactic isoniazid (INH) but should continue INH therapy after transplantation with careful monitoring of liver function tests and cyclosporine or tacrolimus levels. Some clinicians administer prophylaxis only to patients with risk factors, including recent skin-test conversion, a history of active TB, abnormalities on chest radiograph, the presence of other immunosuppressing conditions such as malnutrition, and Asian, African, or Native American heritage [6].

It may be tempting to try to use a short-course prophylaxis regimen, such as the combination of rifampin/pyrazinamide administered over a 2-month period. However, recent reports of the hepatotoxicity of this combination are worrisome, and it is best avoided in pretransplant patients [19].

LATENT FUNGAL INFECTION

The endemic mycoses histoplasmosis and coccidioidomycosis may reactivate in patients who have resided in the midwestern and southwestern United States, respectively. Serological screening and secondary prophylaxis for coccidioidomycosis in transplant recipients have been recommended for transplant candidates and recipients in areas where these diseases are en-
demic, because approximately half of coccidioidal infections in transplant recipients are due to reactivation of preexisting disease [10]. As yet, however, screening for past exposure to histoplasmosis has not been routinely recommended. The presence of calcified hilar nodes and splenic calcifications may be indicative of past histoplasmosis or other granulomatous disease and should be considered if the patient develops a febrile illness after transplantation.

Aspergillus species respiratory colonization per se is not generally considered to be a contraindication to lung transplantation but should prompt a thorough search for active disease, including chest CT scan, and any active disease should be treated to full radiographic resolution before consideration of possible transplantation. Patients with cystic fibrosis, marijuana users, and farmers are particularly likely to be colonized pretransplant. Although Aspergillus species colonization is a risk factor for infection after transplantation, only a fraction of colonized patients will develop active infection. Randomized trials of pretransplant antifungal therapy for Aspergillus species–colonized patients have not been done, and many centers rely on posttransplant prophylaxis or preemptive therapy as strategies for the prevention of invasive fungal infection [20].

Screening for and eradicating candidal urinary tract infections may be useful for renal or pancreas transplant candidates, given the risk of developing upper tract disease or intraabdominal infections after transplantation [6, 21]. Liver transplant candidates at some centers receive selective gut-decontamination protocols to reduce the likelihood of posttransplant bacterial and fungal infections from an intestinal source; mycostatin is a popular component of such regimens [22].

**LATENT PARASITIC INFECTION**

Toxoplasmosis reactivation after transplantation is uncommon, and the highest risk situation is when a Toxoplasma species–seronegative recipient receives a heart from a Toxoplasma species–seropositive donor. Heart recipients are at highest risk, because the organism encysts in myocytes. Serological screening of the recipient can identify seronegative individuals at potential risk who should receive pyrimethamine prophylaxis after transplantation if they are not receiving trimethoprim-sulfamethoxazole for Pneumocystis carinii pneumonia prophylaxis [23].

Strongyloidiasis may persist at low levels in the intestines of recipients who have lived in areas where strongyloidiasis is endemic (many areas of the tropics and the southeastern United States.) Strongyloides species hyperinfection and dissemination can occur when such an individual receives transplant-level immunosuppression [6]. Although practices at different centers have varied, serological screening of international transplant candidates and those who have lived in areas where infection is endemic would appear to be reasonable. Serological testing is more sensitive than 3 stool exams for ova and parasites, although the latter are used by some centers.

Although Trypanosoma cruzi, the agent of Chagas disease, is not common in the United States, there are reports of its transmission by blood transfusion and by transplantation, as well as reactivation of prior disease [24]. If a transplant candidate has resided in an area of South America where Chagas disease is endemic, then it is reasonable to screen for T. cruzi by serological testing and to monitor for reactivation after transplantation.

**LATENT VIRAL INFECTION**

One of the best-known uses of recipient serological screening is testing for CMV serostatus. Although the limited supply of available organs does not allow for serological matching for CMV, the donor and recipient’s serostatus frequently determines what CMV prophylaxis or monitoring and preemptive therapy will be used [6, 25]. Because the donor-seropositive, recipient-seronegative (D+/R−) combination represents the highest risk for severe CMV disease, high virus loads, CMV recurrence, and ganciclovir resistance, this group merits especially intensive efforts at CMV prevention [25–27].

Viral screening for other members of the herpesvirus family also provides useful information. Although some centers screen for herpes simplex virus (HSV)–1 seropositivity, others administer antiviral therapy to all recipients at least for the first month after transplantation, using agents such as ganciclovir or acyclovir with activity against HSV. Approximately 90% of adults are seropositive for varicella-zoster virus (VZV), but those few who are seronegative are at risk for primary varicella after transplantation, which can be severe. If time prior to the anticipated transplantation permits, varicella vaccination of seronegative candidates is desirable.

Epstein-Barr virus (EBV) is associated with the devastating disease known as posttransplant lymphoproliferative disease (PTLD). The highest risk for PTLD is found in the EBV D+/R− combination, a situation similar to that in CMV infection. However, as with CMV, EBV-seropositive recipients can also reactivate virus, especially under the influence of intensive immunosuppression such as antilymphocyte therapy. With recently published strategies for EBV-PCR monitoring of high-risk patients, and potential intervention in the form of antiviral therapy and reduction of immunosuppression, there is now more reason than ever to determine donor and recipient EBV serostatus [28, 29]. Centers that have traditionally not included such determinations should consider modifying their practice to do so.

Human herpesvirus (HHV)–6 is emerging as a virus with
significant consequences after transplantation, including its role as a cofactor for CMV effects, risk for fungal infections, and possibly allograft dysfunction [30]. However, because ~95% of adults are seropositive for HHV-6, no recommendations have yet emerged for serological screening prior to transplantation. Whether such screening would be more useful in pediatric candidates, who might be more likely to be seronegative, is a question for future research.

There is increasing literature on HHV-8 infection in transplant recipients. The incidence of this infection appears to vary by geographic region. Clinically evident Kaposi sarcoma (KS) appears to be the result of reactivation of HHV-8 in most patients, although it can also be transmitted from the donor [31, 32]. As yet, no specific antiviral therapy has been advocated for prophylaxis or preemptive therapy, and routine screening has not yet been recommended. Although many centers have considered a history of KS be a contraindication to transplantation, one recent report described a patient with a history of KS who successfully underwent retransplantation without evidence of recurrence of KS [33].

HIV screening is done routinely by transplant centers and has been considered to be an absolute contraindication to transplantation until recently, when some centers have reassessed the question of whether transplantation may be a viable strategy in the HIV-positive recipient with a well-controlled virus load who is receiving HAART [34]. A multicenter trial is ongoing. A host of medical and ethical questions remain to be addressed regarding this topic, and such transplantations should be considered investigational at this point.

Many centers screen for human T-lymphotropic virus (HTLV) I and II. HTLV-I is a retrovirus that is endemic in certain areas of the Caribbean and Japan and can cause tropical spastic paraparesis or adult T cell leukemia/lymphoma, but seropositive individuals are frequently asymptomatic for decades and may never develop disease at all. HTLV-II is a related virus that is difficult to distinguish by serological testing and is not currently known to be associated with any disease. HTLV-I–associated myelopathy and leukemia/lymphoma have been reported to occur by reactivation after transplantation, but, in one report, 16 HTLV-I–seropositive kidney recipients did not develop disease [35]. Although the detection of HTLV-I/II seropositivity has often been considered a contraindication to transplantation, the fact that there is little literature on the magnitude of the risk of progressing to overt disease under the influence of immunosuppression could mean that management can be individualized, particularly for the potential recipient of a lifesaving transplant.

Hepatitis viruses are a major topic in transplantation and have been reviewed elsewhere [36, 37]. HCV-seropositive recipients of a liver transplant for end-stage hepatitis C frequently have recurrence of hepatitis C in the transplanted organ yet overall have improved survival and clinical courses, compared with HCV-infected patients who receive treatment without transplantation. HCV-seropositive recipients of nonhepatic transplants are at higher risk for progressive liver disease and other complications such as sepsis after transplantation, but careful analyses of HCV-seropositive renal transplant recipients reveal that transplantation does improve outcome, compared with continuation of dialysis [38]. The role of pretransplant virus load reduction is under investigation.

Hepatitis B surface antigen (HBsAg)–positive patients undergoing nonhepatic transplantation are at risk for active or even fulminant HBV after transplantation and have been considered poor candidates for transplantation until recently. However, there are long-term survivors from the early era of transplantation who have functioning renal allografts and functioning livers, despite detectable HBV-DNA virus loads [39]. The availability of lamivudine and other agents active against HBV may transform the outlook for these potential recipients, although the optimal timing of antiviral therapy and the role of pretransplant virus load reduction is under investigation. Liver transplantation done for end-stage disease due to hepatitis B have been the subject of intensive investigation as to the optimal use of hepatitis B immunoglobulin (HBIG) with or without antiviral therapy for prevention of HBV reactivation after transplantation [40, 41].

The use of hepatitis B core antibody–positive, HBsAg-negative donors is a complex topic covered in more detail elsewhere [1, 2]. Most centers use such organs in recipients of nonhepatic transplants with or without prophylactic HBIG and antiviral therapy, but there is general agreement that such a transplantation is safer when done for a recipient who has received HBV vaccine. HBV-seronegative recipients undergoing pretransplant screening should receive the hepatitis B vaccine. The classic series, consisting of doses at 0, 1, and 6 months, may be modified given the time available before transplantation, and consideration should be given to the use of higher potency doses in patients undergoing dialysis who may have suboptimal responses to standard doses of HBV vaccine [42].

Although BK and JC papovaviruses and parvovirus B19 cause important diseases after transplantation, screening has not yet become routine prior to transplantation. BK virus allograft nephropathy is a recently described condition that can lead to allograft dysfunction and loss. BK virus is a member of the polyomavirus family and may be found colonizing asymptomatic individuals. As yet, no recommendations have emerged for pretransplant screening. Although graft loss due to BK virus is a devastating complication, there is one recent report of successful retransplantation after BK infection [43]. Recent reports
the goal of minimizing posttransplant risks by increasing patient knowledge. This decompresses somewhat the immediate posttransplant period, in which patients are besieged with infection risks to patients, families, and physicians outside the transplant center.

PRETRANSPLANT IMMUNIZATION

As discussed above, the pretransplant screen may uncover a lack of immunity to important pathogens from which primary infection after transplantation could prove devastating. In addition, vaccinations after transplantation are likely to be less effective than when given prior to transplant-level immunosuppression [42]. Patients who are seronegative for VZV or HBV should receive these vaccinations, with the caveat that VZV vaccine is a live attenuated vaccine and should not be given if transplantation is expected to occur imminently. Patients who have not received a pneumococcal polysaccharide vaccine within the past 5 years (or the past 2 or 3 years, according to some clinicians) should receive that vaccine, because posttransplant pneumococcal sepsis, pneumonia, and meningitis can occur. Tetanus-diphtheria status should be updated with a booster if necessary, according to standard guidelines. Liver transplant candidates in particular should be vaccinated against hepatitis A if they are seronegative, preferably before they progress to end-stage liver disease, at which time the response to the vaccine is diminished.

PRETRANSPLANT EDUCATION

The pretransplant time period should be viewed as an ideal opportunity for patient education, including a broad outline of the infections to which the transplant recipient may be susceptible and a rationale for the preventive strategies in use at that particular center. Regularly scheduled pre- and posttransplant classes and support group sessions are an excellent venue for such educational activities. The importance of compliance with medications, including infection prophylaxis, should be emphasized. Food and environmental exposures, pets, and other potential sources of infection should be discussed, with the goal of minimizing posttransplant risks by increasing patient knowledge. This decompresses somewhat the immediate posttransplant period, in which patients are besieged with information while recovering from a major surgical procedure.

The pretransplant screening evaluation is also an opportunity to communicate with the patient’s primary physician(s). Because, nowadays, many patients’ home communities may be distant from the transplant center, it may be impractical for the transplant center to provide all care face to face. The provision of information to the primary physician can be extremely helpful in terms of communication, triage decisions, and early detection of complications including infections. Available reviews of transplantation infectious-disease–related issues targeting the primary physician [7, 45] can be included in communications sent to these individuals. The goal is not to replace functions that should be carried out by the transplant center but rather to help local clinicians be a more educated and effective part of the patient’s treatment team.

CONCLUSIONS

The pretransplant evaluation is an important phase in the process of transplantation. Screening the potential recipient for active and latent infections may determine whether the recipient qualifies for transplantation at the current time or may influence what prophylaxis and monitoring the recipient receives after transplantation (in conjunction with donor serologic testing). Vigorous treatment of any active infection prior to transplantation, to the extent possible, is axiomatic. The pretransplant period is also an ideal time to assess and update vaccination status as well as to provide education regarding infection risks to patients, families, and physicians outside the transplant center.

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