Most transplant centers have adopted a multidisciplinary team approach to ensure that patients who have received solid-organ transplants are cared for efficiently and comprehensively. Similarly, the 2013 American Transplant Congress provided a symposium to benefit a diverse group of healthcare professionals that included transplant coordinators, nurses, pharmacists, dieticians, and physicians who interact with transplant recipients in either the acute or ambulatory setting.

This panel session reviewed common issues that arise in the long-term management of transplant recipients, both to update the aforementioned clinical caregivers and to promote discussion and exchange of practices among healthcare professionals in different practices. Specifically, experts addressed the use of newer immunosuppressive agents and the management of infectious diseases and hypertension post transplant. Additionally, experts explored alcohol use in the transplant recipient as well as screening and primary prevention in the transplant recipient.

**IMMUNOSUPPRESSION: IN WITH THE NEW, OUT WITH THE OLD**

Based on a presentation by Steven Gabardi, PharmD, FCCP, BCPS, Abdominal Organ Transplant Clinical Specialist, Brigham and Women’s Hospital, Boston, Massachusetts.

Despite short-term patient and graft-survival benefits afforded by modern immunosuppressants, their unfavorable safety profile poses a significant long-term challenge. Infectious, metabolic, cardiovascular, renal, and hematologic toxicities ultimately impede graft and patient survival in the long run. Thus, clinicians have focused on enhancing currently available immunosuppressive agents or using drugs currently approved for other indications within the transplant setting. Further, newly emerging immunosuppressive therapies on the horizon include agents that target both cellular and humoral pathways.

**Issues with Modern Immunosuppression**

Modern immunosuppressants have made significant progress in preventing acute cellular rejection (ACR) and improving short-term allograft survival, but the impact on long-term outcomes is lacking. For instance, as compared with the past decade, allograft survival at 1 and 3 years has increased by 5% and 6%, respectively. However, longer-term survival rates have improved only marginally over the past 20 years. Modern desensitization agents have practically eliminated hyperacute rejection. Nevertheless, antibody-mediated rejection (AMR) is a significant complication after highly sensitized transplantation, occurring in about 35% of all cases.

The use of current immunosuppressive agents also is associated with considerable side effects and poor tolerability. In particular, cardiovascular and renal complications remain chronic issues as transplant patients age. Cardiovascular disease is still the most common cause of death among patients with a functioning allograft.

In the design of novel immunosuppressants, the ideal drug would be selectively effective, formulated for ease of admin-
istration and compliance, and associated with favorable safety and pharmacokinetic profiles. However, because there is no “perfect drug,” a more feasible goal may be to improve on currently available therapies.

Recycle, Repurpose, Reuse

Immunosuppressive agents can be recycled through reformulation. For example, a once-daily, extended-release form of tacrolimus was recently approved by the US Food and Drug Administration (FDA) to improve pharmacokinetics and medication adherence in patients who have received a kidney transplant.

When compared with twice-daily tacrolimus, an extended-release formulation has the potential advantages of convenient once-daily dosing, improved systemic absorption or bioavailability, limited interpatient variability, and reduced peak-to-trough fluctuation. These advantages are a result of a proprietary technology that incorporates drug substances with low water solubility into a “meltable” extended-release vehicle. The outcome is much improved absorption and controlled release of the active drug. Initial studies have shown that switching to once-daily tacrolimus can be accomplished successfully while maintaining graft protection. Switching also has proven effective in managing tremors associated with twice-daily tacrolimus.

The term “repurpose” refers to modifying the use of drugs currently approved for non-transplant indications by applying them, off-label, in the transplant setting. This method is exemplified in AMR postmarketing surveillance. One-year pharmacokinetic and pharmacodynamic data suggest that trough VCS concentrations of 35–60 ng/mL should be used to optimize the drug’s efficacy versus its toxicity. VCS should be given on an empty stomach, since absorption is reduced when it is taken with meals. Mild-to-moderate hepatic impairment may lead to a significant increase in VCS exposure.

Other drugs in the research pipeline also are being investigated as targets for humoral pathways.

Belimumab is a humanized monoclonal antibody against B-cell–activating factor (BAFF), also known as B-lymphocyte stimulator (BLYS), a mediator essential for B- and plasma-cell survival. A clinical trial that investigated the effectiveness of belimumab in decreasing antibody levels in sensitized patients awaiting kidney transplantation was terminated due to a lack of efficacy. A phase II pilot study currently is under way to assess belimumab versus placebo when added to the standard of care to prevent rejection.

Studies also are assessing the efficacy of C1 esterase inhibitors in preventing and treating AMR. These agents may prevent complement-mediated allograft injury during AMR by inhibiting the first component within the complement system.

Tocilizumab is a humanized, monoclonal antibody against the interleukin-6 receptor. The agent may prove beneficial in pancreatic islet-cell transplantation because inflammation is a key mediator of islet-cell dysfunction and destruction. Initial evidence has suggested that tocilizumab decreases blood glucose and
glycosylated hemoglobin levels in diabetic patients and reduces islet-cell death.29

**Summary**

The future hopefully will bring novel immunosuppressive therapies that offer favorable safety profiles, unique and improved mechanisms of action, and superior efficacy in prolonging long-term allograft survival. The focus of transplantation research has shifted to revamping current immunosuppressants and/or applying drugs approved for other indications to prevent allograft rejection. Overall, the ultimate goal is to curtail toxicities to enhance long-term outcomes.

**INFECTIOUS DISEASES: SURVEILLANCE, TREATMENT, AND OUTCOMES**

Based on a presentation by Marian Michaels, MD, MPH, Professor of Pediatrics and Surgery, Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania.

With the development of new antivirals over the past couple of decades, significant advancements in preventing and treating infections in organ transplant recipients have been made. Nonetheless, infections continue to cause considerable morbidity and mortality post transplant. Infectious disease will remain a major morbidity and mortality post transplant. Infections continue to cause considerable complications affecting allograft function due to preexisting conditions and nosocomial exposures also predispose recipients to infections.

**Predisposing Factors for Infection After Solid-Organ Transplant**

Risk factors for transplant-related infections can be broadly classified as pretransplant (recipient- or donor-derived), intraoperative, and post transplant.28 Pretransplant risk factors attributed to the eventual recipient include the type of organ being transplanted, as this may predict the most likely site of infection. Underlying illnesses that lead to organ failure, such as cystic fibrosis, hepatitis C virus (HCV) infection, and hepatic cirrhosis, increase the risk of infection. Other recipient-related pretransplant risk factors include greater severity of the underlying disease for which the transplant is intended to resolve, chronic malnutrition, mechanical ventilation, extremes in age, and a lack of preexisting immunity and vaccination. Donors also can impact pretransplant risk factors for infections.

Intraoperative factors, such as a prolonged operative time, unexpected surgical complications, excessive bleeding, or need for blood products, all increase the risk of postoperative infections in these patients.

Post transplant, the net state of immunosuppression is the primary risk factor for infection after solid-organ transplant. Aside from immunosuppression, technical complications affecting allograft integrity are major risk factors that often manifest as abscesses or infections within the allograft tissue post transplant. Prolonged placement of indwelling cannulae and nosocomial exposures also predispose recipients to infections.

**Timeline of Infections in Solid Organ-transplant Recipients**

The timing of infections post transplant can guide clinicians toward identifying the most likely pathogens and differential diagnosis (Figure 1).28,29 A relationship exists between various stages post transplant and the epidemiologic exposures and immunosuppression strategy. The early post-transplant setting extends from 0 to 30 days after surgery. This first phase is characterized by bacterial or yeast infections due to preexisting conditions or colonization in the recipient, donor factors, or complications of surgery. Surgical-site infections are common, and graft injuries occurring in this period can later serve as a nidus for abscesses. Conversely, opportunistic infections are generally absent during this interval.

The second phase (between 30 and 180
days after surgery) is known as the intermediate interval post transplant. Fever during this period is mostly attributed to latent pathogens, including polyomavirus, adenovirus, recurrent HCV, or endemic fungi, which are reactivated within the recipient. In contrast to previous decades, opportunistic infections caused by *Pneumocystis jirovecii*, *Listeria monocytogenes*, and *Toxoplasma gondii* are no longer common due to prophylaxis with sulfamethoxazole and trimethoprim. Likewise, herpesvirus infections now occur infrequently due to antiviral prophylaxis. However, in the absence of prophylaxis, the aforementioned opportunistic infections and cytomegalovirus (CMV) infections will prevail in the intermediate period.

The final, or late, phase of post-transplant infections extends past 180 days. In general, infectious risk is low due to minimization of immunosuppression and stable graft function. However, late CMV and opportunistic infections now can appear, as prophylaxis against these infections generally is completed by this phase. The presence of community-acquired respiratory and gastrointestinal viral pathogens also is common.

Some infectious microorganisms prevail throughout the entire post-transplant course. Nosocomial pathogens and *Clostridium difficile* colitis also can present irrespective of time after transplant.

**Donor-derived Infections**

Due to advancements in donor screening, an unanticipated transmission of an infection from a donor is seen rarely. However, the few cases that do occur often are coupled with significant morbidity and potential mortality. As a result, transplant surgeons and clinicians should have an understanding of the epidemiology of potential donor-derived infections. Transmission of latent microorganisms such as herpesviruses, HCV, *Toxoplasma* sp, mycobacteria linked to tuberculosis, and endemic fungi from asymptomatic donors are most common, and infections related to these organisms typically present late post transplant. On the other hand, donor-derived bacteria, West Nile virus, or rabies virus generally lead to acute symptomatic infections in transplant recipients.

When determining whether or not to initiate prophylaxis against donor-derived infections, clinicians must consider several questions. For example, is there a safe, effective prophylactic agent available? If not, the risk of prophylaxis may outweigh the potential benefit. Are there alternatives to pharmacologic prophylaxis (eg, preemptive prophylaxis), and how does the effectiveness of these alternative methods compare with that of universal prophylaxis? If there is a transplant population that is most at risk, then prophylaxis may be limited to this group of recipients. Finally, the duration of prophylaxis is an area of continued debate. Is there a period of time when the risk of infection is at a peak? Such an interval could be used as a guide for determining the duration of prophylaxis.

**Strategies for Safe Living and Preventative Measures**

All patients and family members should be educated on strategies for preventing infectious diseases or minimizing exposure after solid-organ transplant. Performing careful exposure histories and physical examinations, along with updating the patient’s immunization status, is an important pretransplant measure. In addition, vaccination remains essential post transplant for both the recipient and the people with whom the recipient will be in direct contact.

Direct contact, ingestion, and inhalation are the most common means of transmitting infectious diseases. Hence, patients and family members must be instructed on safe practices, such as washing their hands thoroughly and frequently and avoiding contact with sick persons or crowded areas. In addition, recipients must be aware of foods to avoid, such as unpasteurized, raw, or undercooked products. Lastly, travel safety is key in abating the risk of infectious diseases after solid-organ transplant. Patients should discuss all travel arrangements with their healthcare team at least 2 months before departure. Up-to-date travel advisories specific to different travel areas can be obtained from the Centers for Disease Control and Prevention website (www.cdc.gov/travel).

**Summary**

Infections cause considerable morbidity and mortality in recipients of solid-organ transplants. Over the years, specific recipient/donor risk factors, timing, and pathogens have been identified in this population. A clear understanding of these universal themes can ensure effective management of infections after solid-organ transplant. Moreover, because significant complications of transplant-related infections may endanger both graft and patient survival, pre- and post-transplant prevention should be emphasized.

**HYPERTENSION: BEST PRACTICES FOR MANAGEMENT POST TRANSPLANT**

**Based on a presentation by Deborah Hoch, DNP, ACNP-BC, Nurse Practitioner, Transplantation, Maine Medical Center, Portland, Maine.**

Hypertension poses a significant and common challenge after transplantation. Only 5%–12% of renal transplant recipients are normotensive at 1 year. The detrimental effects of poorly controlled blood pressure are reflected post transplant, since cardiovascular disease remains the most common cause of death in patients with a functioning allograft. Kasiske and colleagues identified hypertension as an independent risk factor for allograft failure and reduced patient survival. Accordingly, controlling blood pressure can improve both allograft and patient survival. Therefore, managing hypertension is crucial in prolonging survival and augmenting long-term outcomes post transplant.

**Risk Factors for Hypertension and Resistant Hypertension**

Several risk factors have been associated with the development of post-transplant hypertension (Table 1). Resistant hypertension, defined as blood pressure that remains above goal despite the concurrent use of three antihypertensive agents of different classes, also
is common in transplant recipients, because the majority have multiple risk factors for hypertension. Key players in the development of resistant hypertension post transplant include the presence of pretransplant hypertension and immunosuppression-related factors such as CNI-induced vasoconstriction and corticosteroid-induced sodium and fluid retention.

Guidelines and Goals

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines are universally used to help control blood pressure after transplantation. For adult transplant recipients, the guidelines recommend that blood pressure be reduced to a goal systolic blood pressure of < 130 mm Hg and diastolic blood pressure of < 80 mm Hg. Due to the lack of data from randomized controlled clinical trials regarding the treatment of hypertension post transplant, the KDIGO guidelines do not recommend a specific preferable class of antihypertensive agents for long-term therapy. Nevertheless, clinicians can tailor antihypertensive therapy to address other comorbid conditions also present in the post-transplant patient.

Clinical Pearls for Hypertension Management in Transplant Recipients

Diet can impact blood pressure, and dietary modifications can induce lower blood pressure. The Dietary Approaches to Stop Hypertension (DASH) is a particularly effective eating plan stressing the importance of weight loss, reduced salt intake, and moderate alcohol consumption. This plan should be extrapolated to the post-transplant population. Sodium restriction lowers systolic blood pressure after renal transplantation, thereby improving long-term outcomes.

Medical management of blood pressure post transplant typically requires the use of at least two antihypertensive agents from different therapeutic classes. In general, dihydropyridine-based calcium-channel blockers (CCBs) are the most widely used initial antihypertensive agents in transplant recipients, because they effectively lower blood pressure by dilating efferent arterioles and counteracting CNI-induced vasoconstriction of glomerular arterioles. The use of a dihydropyridine CCB post transplant can lead to improvement in glomerular filtration rate (GFR) and reduction in allograft failure.

Although angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs) generally are avoided immediately after renal transplant to prevent a confounding rise in serum creatinine concentration, these drug classes are preferred in the setting of post-transplant erythrocytosis (PTE) or proteinuria. In addition, recent evidence suggests that these therapies provide a survival benefit after renal transplant.

Erythrocytosis post transplant has been attributed to growth factors such as angiotensin II on erythroid progenitors. Therefore, inhibiting the renin-angiotensin system with an ACEI or an ARB is the most effective treatment strategy for PTE. For proteinuria, the KDIGO guidelines recommend first-line therapy with an ACEI or an ARB, since these drugs mitigate proteinuria and may halt the progression of renal disease. On the other hand, ACEIs and ARBs should be used cautiously in patients with anemia and hyperkalemia post transplant.

In the setting of chronic fluid retention or increased sodium intake, diuretics are effective treatment modalities. However, agents acting at the loop of Henle are preferred over thiazide diuretics when the GFR is < 30 mL/min. Moreover, a nonselective β-adrenergic receptor antagonist such as propranolol is often preferred in transplant recipients with CNI-induced tremors.

Summary

Hypertension remains a major challenge after transplantation, particularly when renal transplant recipients are considered. To minimize cardiovascular risk and improve patient and allograft survival, systolic blood pressure should be lowered to < 130 mm Hg and diastolic pressure to < 80 mm Hg with appropriate antihypertensive agents. Diet modifications continue to play an essential role in managing hypertension post transplant. Unfortunately, guidelines outlining a specific antihypertensive class of choice for transplant recipients are lacking. Nevertheless, certain agents may be more effective and thus may be preferred based on the clinical situation or presence of specific comorbidities.

ALCOHOL USE BY TRANSPLANT RECIPIENTS

Based on a presentation by Paolo DeSimone, MD, PhD, Unità Operativa Chirurgia Generale e Trapianti di Fegato, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy.

Some healthcare professionals in the transplant community instruct all their patients to avoid consuming alcohol completely, regardless of the type of organ transplanted, whereas others permit occasional “social” drinking. The one exception are recipients of liver transplants, since alcoholic cirrhosis may result from regular consumption of even small amounts of alcohol. No guidelines or hard-and-fast rules exist regarding alcohol consumption post transplant. Nevertheless, educating transplant patients regarding alcohol consumption may deter excessive use.

Making Your Patient ‘Drink Aware’

Reeducating transplant recipients is essential to ensure that they make informed decisions about drinking beer, wine, or other alcoholic beverages after transplantation. Transplant clinicians should define what exactly comprises a

---

**TABLE 1**

Risk Factors for Hypertension Post Transplant

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allograft rejection</td>
</tr>
<tr>
<td>Delayed and/or chronic allograft dysfunction</td>
</tr>
<tr>
<td>Deceased donor allografts</td>
</tr>
<tr>
<td>Calcineurin inhibitor-induced vasoconstriction</td>
</tr>
<tr>
<td>Corticosteroid-induced sodium and fluid retention</td>
</tr>
<tr>
<td>Increased body weight</td>
</tr>
<tr>
<td>Presence of native kidneys</td>
</tr>
<tr>
<td>Pretransplant hypertension</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
</tr>
</tbody>
</table>

Source: Béji et al.36 Ducloux et al.37

---
“standard” drink. In the United States, a standard drink contains 14 g of pure alcohol. This equates to 12 oz of beer (5% alcohol by volume), 5 oz of wine (12% alcohol), or 1.5 oz of hard liquor or spirits (40% alcohol). Additionally, it is essential to erase the misconception that alcohol may harm only the liver. Instead, healthcare professionals should stress that alcohol affects every organ of the body. There is limited evidence detailing the risk of having an occasional alcoholic beverage after transplant, but there is no risk associated with abstaining.

Data Assessing Alcohol Consumption After Transplant

An estimated 50% of renal transplant recipients consume some amount of alcohol after transplant.47 Lucey and others48 reported that following liver transplant, resumption of heavy drinking did not affect short- or mid-term survival, although it did hamper long-term survival. On the other hand, the evidence did not show that moderate drinking resulted in a negative health impact.

The results of a study by Zelle and colleagues49 suggested that moderate alcohol consumption (10–30 g per day) could protect renal allograft function by reducing the prevalence of NODAT after transplantation and may reduce the risk of mortality in renal transplant recipients, which is in line with findings in the general population.

Summary

Given the lack of data and guidelines, it is difficult to make a single definitive recommendation against occasional alcohol consumption after transplant. However, to deter excessive alcohol consumption, patients should be educated regarding general alcohol consumption and the potential associated risks post transplant.

PRoMARY PREVENTION: SCREENING PROTOCOLS FOR TRANSPLANT RECIPIENTS

Based on a presentation by Mark Burns, DNP, Instructor of Medicine, Mayo Clinic, Gilbert, Arizona.

Because of the toxicities associated with immunosuppression, transplant recipients may experience worsening of preexisting medical conditions and the development of post-transplant complications. Primary prevention is crucial to ensure that these complications do not hinder patient or allograft survival. With continued healthcare reform, transplant practitioners also must learn to manage healthcare costs through preventive medicine. For example, this can be achieved by developing screening protocols for common post-transplant complications. Screening protocols often are used to prevent infectious disease and malignancy post transplant. However, transplant recipients still struggle with obesity after transplant.

Obesity in the Transplant Recipient

When compared with transplant recipients of normal body weight, obese transplant recipients have an increased risk of postoperative complications, including wound infections, delayed graft function, cardiac disease, and graft failure, and increased medical costs. In addition, obesity itself is a common complication after solid-organ transplant, with up to 60% of renal transplant recipients and 20% of liver transplant recipients becoming overweight or obese.50,51

Most transplant centers lack formal weight-loss programs. Therefore, nurses, pharmacists, and other healthcare practitioners involved in the long-term care of transplant recipients need to combat obesity via education and counseling.52 When obesity is identified, first-line therapy still consists of dietary and lifestyle modifications; pharmacologic therapy then may be used adjunctively. When indicated, more extreme measures such as gastric bypass surgery, banding, and sleeve gastrectomy have proven successful in selected individuals.53

Summary

Evidence strongly demonstrates the impact of post-transplant complications such as obesity, malignancy, infections, and cardiovascular disease on transplant patients and allograft survival. Therefore, the focus of healthcare personnel should shift to preventing post-transplant complications or at the least, detecting and managing these complications earlier. The use of screening protocols can help determine at-risk populations to allow for early action and subsequent prevention.

REFERENCES


11. Stegall MD, Diwan T, Raghavaiah S, et


