Chapter 109: Solid-Organ Transplantation

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KEY CONCEPTS

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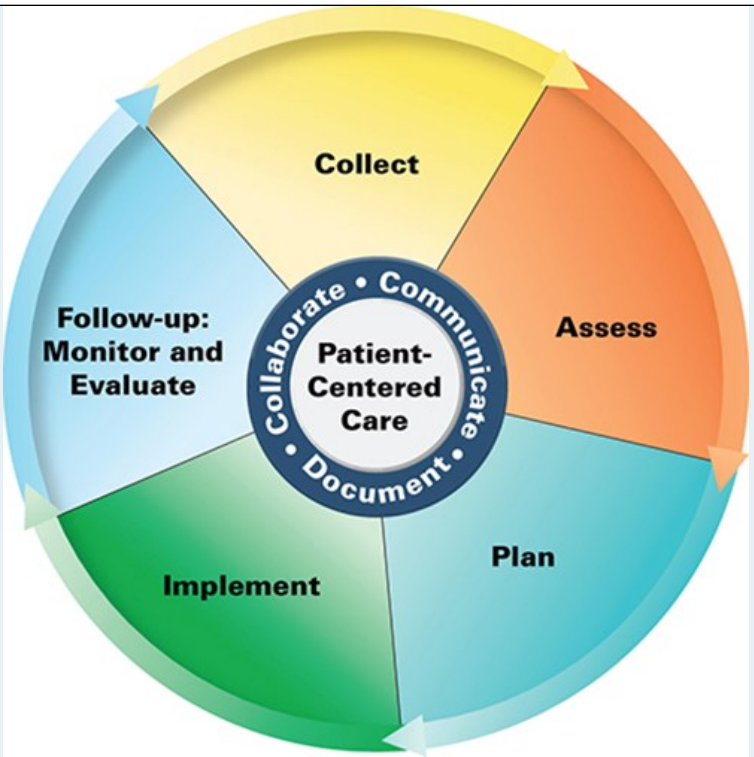
1. Generally, patients receive a combination of two to four immunosuppressive drugs in order to minimize individual drug toxicities as well as block different pathways of the immune response.
2. Antibody preparations that target specific receptors on T cells are classified based on their ability to deplete lymphocyte counts. Most lymphocyte-depleting antibodies are associated with infusion-related reactions, whereas non-depleting agents are generally well tolerated.
3. While the calcineurin inhibitors (CNI) tacrolimus and cyclosporine are the backbone of most immunosuppressive regimens, they are associated with serious adverse effects.
4. Calcineurin inhibitor-induced nephrotoxicity is one of the most common adverse effects observed in solid-organ transplant recipients. Therapeutic drug monitoring is used to optimize the use of calcineurin inhibitors and limit toxicity.
5. Corticosteroids are often a component of immunosuppressive protocols. Their adverse effects have led to steroid-minimizing and steroid-free immunosuppressive regimens. Corticosteroids, however, remain a first-line treatment for allograft rejection.
6. Azathioprine and mycophenolic acid derivatives inhibit T-cell proliferation by altering purine synthesis. Bone marrow suppression is the most significant adverse effect associated with these agents.
7. Sirolimus and everolimus inhibit the mTOR (mammalian target of rapamycin) receptor, which alters T-cell responses to IL-2. The adverse effects associated with these agents include leukopenia, thrombocytopenia, anemia, hyperlipidemia, and impaired wound healing.
8. Immunosuppressive agents are frequently involved in drug-drug and drug-food interactions; thus careful assessments of entire drug regimens are paramount.
9. Long-term allograft and patient survival are limited by chronic rejection, cardiovascular disease, infection, and malignancy.

PATIENT CARE PROCESS

Patient Care Process for Solid-Organ Transplant Recipient*



Collect

- Patient characteristics (eg, age, sex, pregnancy status)
- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use/marijuana), dietary habits
- Current medications including OTC agents, herbal products, dietary supplements
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), temperature (T), height, weight, O_2-saturation
  - Labs including the measure of end-organ function, hemoglobin (Hgb), platelets, serum creatinine (SCr), immunosuppressant concentrations, white blood cell (WBC) count

Assess

- Presence of over immunosuppression: infectious, adverse drug events
- Presence of under immunosuppression: evidence of end-organ compromise/rejection
- Assess risks based on patient-specific risk factors and time post-transplant

Plan

- Drug therapy regimen including specific immunosuppressive agents, dose, route, frequency, and duration (Fig. 109-3)
- Monitoring parameters including efficacy (eg, signs and symptoms of rejection) and safety (eg, CBC, SCr, constitutional symptoms); frequency and timing of follow-up

- Patient education (eg, purpose of treatment, dietary and lifestyle restriction, drug-specific information, medication administration)
- Signs and symptoms of rejection (urine output, BP, pain, fever) or infection (temperature) (see Table 109-3)
- Self-monitoring for signs/symptoms of adverse effects (see Table 109-6)
- Referrals to other providers when appropriate

Implement

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, CNI concentration, SCr)

Follow-up: Monitor and Evaluate

- Maintenance of graft functions
- Presence of adverse effects (eg, nephrotoxicity, tremor, hyperglycemia, hypertension, nausea, vomiting) (see Tables 109-6 and 109-7)
- Immunosuppressant TDM results (TAC, CSA, SIR, EVR); adjust IS dose as needed
- Patient adherence to treatment plan using multiple sources of information
- Re-evaluate immunosuppression/anti-infective goal of therapy every 3 months

* **New solid-organ transplant recipient in the immediate post-op period.**

** ***Collaborate with patient, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

BEYOND THE BOOK

Visit the International Society for Heart and Lung Transplantation Website <https://ishlt.org>. This Website contains many useful links, including links to many registries that track outcomes in patients who have undergone heart or lung transplantation. Access the International Thoracic Organ Transplant (TTX) Registry Data slides <https://ishltregistries.org/registries/slides.asp>, and review the Adult Heart Transplantation Statistics. Focus on the slides that pertain to immunosuppression regimens and outcomes. This will aid in the ASSESS and PLAN steps in the patient care process.

INTRODUCTION

Solid-organ transplantation provides a potentially life-saving treatment for patients with end-stage kidney, liver, lung, heart, and intestinal diseases. Over 300 US hospitals offer transplant services, and pharmacists are an integral part of the transplant team.[1] In 2016, almost 600 pharmacists were members of the American College of Clinical Pharmacy's Transplant Practice and Research Network, and more than 65% of responding centers have a pharmacist on their transplant teams.[2] The Centers for Medicare and Medicaid Services regulations require that transplant programs have a multidisciplinary team including representatives from medicine, nursing, nutrition, social services, transplant coordination, and a clinician with experience in pharmacology. While the regulations do not specifically state that each center must include a pharmacist, a pharmacist provides the necessary expertise in transplant pharmacotherapy.

Since 1980, over 630,000 transplants have been performed in the United States, with over half being kidney transplants. A recent analysis estimated

that since 1987 over 2.27 million life-years have been saved by transplantation, with an average of 4.3 years per patient.[3] Demand for transplantation continues to grow; since 2010, there has been growth in transplant volume across most all organ types (kidney = 37%, liver = 41%, heart = 52%, lung = 52%).[1] This has been made possible through iterative improvements in the way in which sparsely available organs are allocated to patients with end-stage organ disease. Living donors now account for one-third of all kidney transplants, more than any other organ. Living-donor liver transplantation is also becoming increasingly more common. Efforts to expand the cadaveric donor pool have included relaxation of age restrictions, development of better preservation solutions, deployment of machine perfusion pumps, use of "extended-criteria" and non-heart-beating donors, and the transplantation of split liver allografts into different liver transplant recipients. An increase in deaths related to drug overdose has also resulted in an increased number of organs, often times from donors infected with hepatitis C virus (HCV). With the availability of curative treatments for HCV infection, some transplant recipients may be willing to accept a transplant from and HCV-infected donor. Although controversial, creation of a regulated system for compensating individuals financially for the "donation" of a kidney has been suggested.[4]

Despite these efforts, thousands of people on transplantation waiting lists die each year. Current initiatives to improve organ allocation have included allocation primarily on "medical necessity" versus time on the waiting list. Dialysis can be used for an extended period of time to partially replace the function of the kidneys, and more than half of recent heart transplant recipients receive left ventricular assist devices as a bridge to transplantation. Such life-extending therapies are not readily available for liver and lung transplant candidates, however.

Patient and graft survival rates following transplantation have improved dramatically over the past 30 years as a result of advances in pharmacotherapy, surgical techniques, organ preservation, and the postoperative management of patients (Table 109-1). In this chapter, the epidemiology of end-stage kidney, liver, lung, and heart diseases is briefly reviewed, the pathophysiology of organ rejection is presented, the pharmacotherapeutic options for individualized immunosuppressive regimens are explored in great detail, and the unique complications of these regimens along with the therapeutic challenges they present are discussed.

TABLE 109-1

Organ-Specific Patient and Graft Survival Rates

	Patient Survival (%)		Graft Survival (%)	
Organ	**1 year**	**5 years**	**1 year**	**5 years**
Kidney				
Living donor	97.9	89.4	97.5	85.6
Deceased donor	94.3	80.4	93.2	74.5
Liver				
Living donor	96.2	77.6	93	77.3
Deceased donor	93.8	71.9	92.1	71.9
Heart				
Cardiomyopathy			91.6	79.4
Coronary artery disease			89.1	71.9
Lung				
Single	85.8	35.8	85.4	45.5
Double	83.3	47.3	87.3	55.7

KIDNEY

Etiology of End-Stage Kidney Disease

End-stage kidney disease is defined as a glomerular filtration rate (GFR) of <15 mL/min/1.73 m^2 (0.14 mL/s/m^2) or receipt of renal replacement therapy.[5] The most common causes of end-stage kidney disease (ESKD) leading to transplantation are diabetes, hypertension, glomerulonephritis, and polycystic kidney disease.[6]

Epidemiology

The number of prevalent ESKD patients in 2018 was 785,883, which increased by 3.2% relative to 2017.[7] The adjusted prevalence of ESKD increased to 2,242 cases per 1 million people in 2018 (a new high). The vast majority of patients with ESKD undergo intermittent hemodialysis treatment at a medical

facility, though a growing percent of patients undergo home hemodialysis or peritoneal dialysis. The number of patients on the kidney transplant waiting list as of December 31, 2019, was 101,337 which was relatively unchanged compared to those on the waiting list as of December 31, 2014.[6] In 2019, a total of 24,273 kidney transplants were performed. This was an approximate 10% increase relative to the total number of kidney transplants performed in 2018.[6] This was largely driven by deceased donor transplants secondary to increasing acceptance of organs procured from HCV-positive donors. Patients who do not have compatible living donors are placed onto a national waiting list for a deceased donor kidney. Deceased donor kidneys are allocated by the Kidney Allocation System, which considers patient-specific factors such as time on the wait list or time undergoing dialysis, high degree of immune-sensitization, and patient age.[8,9]

At 1-year and 5-year post-transplantation, graft survival was 95.7% and 83.2%, respectively, among patients who underwent deceased donor transplantation between 2012 and 2014. Alternatively, recipients who underwent surgery in the same time period but received a kidney transplant from a living donor experienced 1-year and 5-year graft survival rates of 96.9% and 91.4%, respectively.[6] Median patient survival after kidney transplantation is 12 years.[10]

Physiologic Consequences of Transplantation

The glomerular filtration rate of a successfully transplanted kidney may be near normal almost immediately after transplantation. In some patients, however, the concentration of standard biochemical indicators of kidney function, such as serum creatinine and blood urea nitrogen, may remain elevated for several days or even weeks to months. Standard formulas used to predict drug dosing rely on a stable serum creatinine and thus may be inaccurate or misleading immediately following transplantation. Although the allograft is able to remove uremic toxins from the body, it may take several weeks for other physiologic complications of ESKD—such as anemia, calcium and phosphate imbalance, and altered lipid profiles—to resolve. The renal production of erythropoietin and 1-hydroxylation of vitamin D may return toward normal early in the postoperative period. Because the onset of physiologic effects may be delayed, continuation of the patient's pre-transplantation vitamin D, calcium supplementation, and/or phosphate binders may sometimes be warranted. Patients should be monitored for hypophosphatemia and hypercalcemia for the first few days to weeks after kidney transplantation.

Delayed graft function (DGF) is characterized by the need for dialysis in the first post-operative week.[11] The incidence of DGF in deceased donor kidney transplantation ranges from 10% to 50% and results in a slower return of the kidney's excretory, metabolic, and synthetic functions. DGF is associated with a prolonged hospital stay, higher costs, difficulty managing immunosuppression, slower patient rehabilitation, and lower graft survival.[12] Other early causes of impaired kidney function such as ureteral obstruction, renal artery stenosis, or other technical vascular complications, thrombosis, or rejection should be distinguished from DGF.

General Immunosuppressive Strategy Considerations

Induction

Potent immunosuppressive agents administered parenterally around the time of transplant surgery are referred to as induction therapies. The goal of administering induction immunosuppression is to prevent early cellular- or antibody-mediated.[13] Induction therapies are antibody preparations given most typically along with high doses of corticosteroids. They can be categorized as depleting or non-depleting.[14] Depleting agents include anti-thymocyte globulin preparations (Thymoglobulin, Atgam) and alemtuzumab, whereas the only non-depleting agent is basiliximab. In 2019, 91% of kidney transplant recipients received induction immunosuppression at the time of transplantation.[6] Among kidney transplant recipients at a higher risk for rejection (eg, those undergoing repeat transplantation or those with pre-formed antibodies against their donor) depleting agents should be preferentially administered due to their superiority at preventing acute rejection.[15-17]

Maintenance

Maintenance immunosuppressive therapies are administered to transplant recipients for the duration of the functional life of their transplanted organ, also with the goal of preventing acute rejection. Maintenance immunosuppression regimens are most commonly composed of different agents targeting different pathways or immune system effector cells to ensure adequate immunosuppression as well as increase drug tolerability. The most commonly deployed agents in maintenance immunosuppressive cocktails include the calcineurin inhibitors, anti-metabolites, mammalian target of

rapamycin (mTOR) inhibitors, co-stimulation antagonists, and corticosteroids.[18] Between the two available calcineurin inhibitors, tacrolimus is more potent and is generally preferred over cyclosporine due to a decrease in the incidence of acute rejection.[19,20] Similarly, mycophenolate is generally the preferred anti-metabolite relative to azathioprine.[21] These drugs will all be reviewed in detail later in this chapter.

In 2019, the vast majority of kidney transplant recipients were initiated on regimens consisting of tacrolimus (a calcineurin inhibitor; CNI), mycophenolate (an anti-metabolite), +/− a corticosteroid.[6] Belatacept, a co-stimulation antagonist that first gained FDA approval for use in kidney transplantation in 2011, has been incorporated into CNI-sparing or CNI-avoiding immunosuppressive regimens in kidney transplant recipients owing to its more tolerable side effect profile and potential to improve long-term patient and graft outcomes.[22,23]

LIVER

Etiology of End-Stage Liver Disease

Noncholestatic cirrhosis (hepatitis C, alcoholic cirrhosis, hepatitis B, nonalcoholic steatohepatitis, and autoimmune hepatitis) is the primary cause of end-stage liver disease, and more than 70% of liver transplant recipients have been diagnosed with one of these conditions.[24] Other indications for transplantation include acute liver failure, autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis. Nonalcoholic steatohepatitis represents a growing indication for liver transplantation, while hepatitis C-related indications are declining.

In general, active substance abuse has been a contraindication to liver transplantation, but given the high mortality for acute alcoholic hepatitis and the current lack of viable treatments, this is an area of growing research worldwide. A number of US centers have expanded transplantation in this patient population.[25] Additionally, active or recent malignancy is a contraindication to any transplantation, with the exception of hepatocellular carcinoma meeting specified criteria for liver transplantation.[26,27]

Epidemiology

According to the CDC National Center for Health Statistics 2018 report, there are 4.5 million adults diagnosed with liver disease in the United States, which resulted in nearly 45,000 deaths attributable to liver disease.[28] In 2019, the total prevalence of patients on the United States liver transplant waitlist was over 25,000. However, only 8,896 patients underwent liver transplantation.[24]

Liver allografts are allocated based on a United Network for Organ Sharing-adapted Model for End-stage Liver Disease (MELD) score.[29,30] This score—which is calculated from the patient's serum creatinine concentration, total serum bilirubin concentration, international normalized ratio, and serum sodium concentration—accurately predicts short-term mortality in patients with cirrhosis. Patients listed for liver transplants are prioritized based on acuity, as measured by MELD score, rather than time on the waitlist.

The median survival after liver transplantation is 11 years and is increasing in recent years. Graft failure occurred in 6.6% of deceased-donor liver transplant recipients at 6 months and 8.9% at 1 year for transplants performed in 2018. Five-year and 10-year patient survival is now 80% and 60%, respectively.[24]

Physiologic Consequences of Transplantation

The physiologic consequences of liver transplantation are complex, involving changes in both its metabolic and synthetic function. Postoperatively, the liver transplant recipient will likely have many fluid, electrolyte, and nutritional abnormalities. Biliary tract dysfunction may alter the absorption of fats and fat-soluble drugs.[31] Poor absorption of the lipid-soluble drug cyclosporine improves after successful liver transplantation and reestablishment of bile flow. Vitamin E deficiency and its neurologic complications are usually reversed after successful liver transplantation. In stable adult liver transplant patients, the concentrations of retinol and tocopherol are similar to those seen in normal healthy subjects, indicating recovery of liver production and excretion of bile salts needed for fat-soluble vitamin absorption. Table 109-2 summarizes the effects of liver transplantation on metabolism and renal elimination that are seen in the immediate postoperative period. Most of these changes resolve as liver function normalizes.

TABLE 109-2

Perioperative Changes in Drug Disposition and Elimination Following Liver Transplantation

	Result	Comment
Serum proteins		
↓ Albumin	↑ Free fraction of drugs usually bound to albumin	Diazepam, salicylic acid binding greater in liver transplant than in chronic liver disease because of endogenous binding inhibitors (up to 45 days post-transplant)
↑ Alpha-1-acid glycoprotein	Lower unbound fraction of drugs	Lidocaine
Metabolism/elimination		
Microsomal enzymes	↑ CYP2E1 activity	Increased drug metabolism (induction)
	↔ CYP2D6	Unaffected
	↓ CYP activity	Decreased drug elimination (inhibition)
Oxidation	Stable	
Conjugation	Normalizes after transplant	
Biliary function	↓ Absorption of lipophilic compounds	
	↑ Cyclosporine metabolites in blood	
Renal elimination	Elimination of gentamicin, vancomycin, cephalosporins less than predicted by serum creatinine	Renal elimination of metabolites limited

General Immunosuppressive Strategy Considerations

Induction

Antibody therapy is seldom used as induction in liver transplantation. In 2019, nearly 80% of liver transplant centers in the United States did not utilize induction therapy (with the exception of corticosteroids) due to the reduced immunogenicity of liver allografts relative to other solid organs.[24] Instead, both basiliximab and anti-thymocyte globulin have been utilized to allow for a delay in the introduction of CNIs in the setting of residual hepatic encephalopathy or renal dysfunction post-transplant.[32-34]

Maintenance

Maintenance immunosuppressive therapy for liver recipients in most transplant centers includes a CNI with an anti-metabolite agent with or without steroids.[24] More than 60% of transplant centers use three initial agents, though regimens consisting of two or four agents have also been utilized.

mTOR inhibitors are infrequently used in maintenance regimens in liver transplant recipients, and use has been muted by an FDA-boxed warning outlining a risk of hepatic artery thrombosis when used within 30 days of transplant.[35] Belatacept is not utilized post-liver transplantation secondary to an increase in mortality following its use.[36]

LUNG

Etiology of End-Stage Lung Disease

End-stage lung disease is generally defined as the inability of the lungs to carry out routine gas exchange.[37] The most common causes of end-stage lung disease leading to transplantation are restrictive lung diseases (eg, idiopathic pulmonary fibrosis, sarcoidosis), cystic fibrosis, chronic obstructive pulmonary disease (COPD), and pulmonary arterial hypertension.[38] The Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation (ISHLT) released an updated consensus document in 2014 outlining recommendations for selecting lung transplant candidates, which dictates that transplantation should only be offered to patients who (1) are at high risk (>50%) of death within 2 years if transplantation is not performed, (2) have a high likelihood (>80%) of surviving at least 90 days post-operatively, and (3) have a high likelihood (>80%) of surviving at least 5-year post-transplant assuming there is adequate lung allograft function.[39]

Epidemiology

There is no universally accepted definition for the diagnosis of end-stage lung disease and thus quantifying the incidence is challenging. Rather, conditions that lead to lung disease may have their own respective stages to quantify disease severity, such as with COPD. The Global Initiative for Chronic Obstructive Lung Disease defines stage 4 lung disease as an FEV_1 of <30% expected.[40] The number of patients on the lung transplant waiting list as of December 31, 2019, was 1,423 which was reduced compared to those on the waiting list as of December 31, 2014 (n = 1,683) due to the increasing rate of lung transplants performed annually.[38] In 2019, a total of 2,759 lung transplants were performed which was an increase of 7.6% relative to 2018.[38] Lung transplants are allocated on the basis of the Lung Allocation Score (LAS), which is calculated using patient-specific factors predictive of survival while on the waitlist as well as factors predictive of survival 1-year post-transplant.[41]

Relative to all other solid-organ transplant recipients, those patients who undergo lung transplantation experience the lowest overall survival at all measured time points.[38] In 2016, data analyzed from the ISHLT registry of all lung transplant recipients who underwent transplant between 1990 and 2014 indicated that median patient survival was 5.8 years.[42] Ten-year survival is approximately 33%.

Physiologic Consequences of Transplantation

In the absence of graft dysfunction, gas exchange and parameters of ventilation (tidal volume, minute ventilation, respiratory rate, etc.) after lung transplantation are generally normal relative to those of an otherwise healthy patient without lung disease. Notable differences in pulmonary physiology and function do exist, however. An impaired cough reflex and impaired mucociliary clearance due to at least partial pulmonary denervation increase the risk of infection.[43] Phrenic nerve injury during complex transplant surgery may lead to diaphragmatic paralysis, which complicates post-transplant rehabilitation and is associated with prolonged hospitalization.[44] Right ventricular dysfunction may be observed in the setting of post-operative pulmonary arterial hypertension (see Chapter 46).[45] Among recipients of single lung transplants (as compared to double lung transplantation), infections may develop in the allograft from a native lung source.[46] The upper airways are also a potential source of pulmonary infection, especially among patients with cystic fibrosis, who are often colonized with multi-drug resistant bacteria prior to transplantation.[47] Allograft dysfunction, regardless of the underlying causes, manifests most commonly as shortness of breath due to impaired gas exchange.

General Immunosuppressive Strategy Considerations

Induction

In 2019, 78% of lung transplant recipients received induction immunosuppression at the time of transplantation.[38] Evidence guiding the selection of induction agents in lung transplantation is often of lower quality. Single-center, retrospective evaluations generally indicate a lower incidence of acute

rejection but a higher incidence of infections among recipients of depleting agents.[48]

Maintenance

In 2019, the vast majority of lung transplant recipients were initiated on regimens consisting of tacrolimus, mycophenolate, and a corticosteroid.[38] Tacrolimus is the only FDA-approved immunosuppressive agent for use in lung transplants, which can complicate lung transplant recipients' access to their necessary, life-sustaining medications.[49]

A serious, immunologically mediated complication post-lung transplantation is the development of bronchiolitis obliterans syndrome (BOS), also referred to as chronic lung allograft dysfunction (CLAD) or chronic rejection. There are no universally effective treatments for the management of BOS, but various therapeutic approaches have promise in preventing its development. These strategies may include the use of mTOR inhibitors in maintenance immunosuppression as well as the addition of azithromycin, montelukast, and even statins into medication regimens.[50-54]

HEART

Etiology of End-Stage Heart Disease

Advanced heart failure (ie, stage D) can be defined in several ways. Typically these patients have advanced symptoms (eg, New York Heart Association class III or IV) despite maximal medical management. Many patients with advanced heart failure will be frequently admitted to hospital, and most cannot tolerate adequate doses of standard heart failure drug therapies such as ACE inhibitors and beta-blockers.[55] Once in the advanced stage of the disease, patients have an expected 1-year mortality risk of 80% or greater without a heart transplant or a left-ventricular assist device implantation.[56] Idiopathic cardiomyopathy and ischemic heart disease account for heart failure in more than 90% of heart transplantation recipients.[57] Other etiologies include uncontrolled hypertension, valvular disease, genetic cardiomyopathy, chronic alcohol abuse, amyloidosis, cardiac sarcoidosis, congenital heart disease, peripartum cardiomyopathy, and retransplantation for graft atherosclerosis or dysfunction. The role of heart transplant as a therapeutic option for patients with heart failure is discussed in Chapter 36.

Epidemiology

From 2008 to 2019, the number of new listings for heart transplant in the United States increased by 42.5%, from 2,867 to 4,086.[57] The number of candidates awaiting heart transplant increased by 42.6% over 2008 to 2019, from 5,304 to 7,562. The median wait time in 2018 to 2019 was 5.1 months, the lowest in the past decade. The number of heart transplants performed in the United States has steadily risen, albeit slowly, and in 2019 was at 3,597. Adult death rates after heart transplant continued to decline; of those who underwent transplant in 2018, 6.4% died by 6 months and 7.9% died by 1 year.[57] The median survival after heart transplant surgery is 12 to 13 years.[58]

Physiologic Consequences of Transplantation

In the native heart, the sympathetic and parasympathetic nervous systems exert powerful control over heart rate and contractile force. During the surgery, the transplanted heart is denervated and no longer responds to physiologic stimuli and pharmacologic agents in a normal manner.[59] In situations requiring an increased heart rate such as exercise or hypotension, the denervated heart is unable to increase heart rate but instead relies on increasing the stroke volume. Later in the course of exercise or hypotension, heart rate increases in response to circulating catecholamines. While the maximum exercise capacity of heart transplant recipients is below normal, most patients are able to resume normal lifestyles and participate in reasonably vigorous activities.[59]

A number of autoregulatory and physiologic responses present in the normal heart are interrupted or blunted for the first 6 weeks after transplantation. The donor sinus node function may be impaired as the result of the preservation regimen, direct surgical trauma at excision, the presence of long-acting antiarrhythmics (eg, amiodarone) taken prior to transplant by the recipient, and a lack of "conditioning" responsiveness to catecholamines.[60] Consequently, the transplanted heart generally requires chronotropic support with either dobutamine, dopamine, or pacing in the perioperative period to maintain a heart rate greater than 110 beats/minute and satisfactory hemodynamics (ie, blood pressure, urine output, and tissue perfusion).[61]

Right ventricular function is frequently impaired, presumably as a result of preservation regimen injury and elevated pulmonary vascular resistance. Common treatments for right-heart failure include intra- or postoperative administration of pulmonary vasodilators (eg, nitric oxide) and inotropic agents like milrinone and dobutamine.[62]

A "restrictive" hemodynamic pattern may be present initially but usually improves in 6 weeks following transplantation. Donor–recipient size mismatch may contribute to early post-transplantation hemodynamic abnormalities characterized by higher right and left ventricular end-diastolic pressures. Tachyarrhythmia (eg, nonsustained ventricular tachycardia) is usually transient and may result from the use of catecholamines or milrinone.

Myocardial depression frequently occurs as a result of non-immune-related graft injury from cold ischemia and generally requires temporary inotropic support with agents such as dobutamine, milrinone, and epinephrine. Severe forms of myocardial depression/injury can manifest as sustained hypotension and low cardiac output—a syndrome known as primary graft dysfunction (PGD)—which can be severe enough to require temporary mechanical circulatory support.[63]

General Immunosuppressive Strategy Considerations

Induction

The available evidence does not suggest a consistent benefit for induction immunosuppression in terms of improving post-transplant survival or reducing rates of acute rejection after heart transplantation. As such, the use of induction therapy is not uniform, and fewer than 50% of heart transplant recipients receive this therapy at the time of surgery.[64] Considerations favoring the use of induction therapy after heart transplantation include high-risk immunologic features (ie, allosensitization) or the need to delay calcineurin inhibitor initiation in the setting of renal injury. Of the available agents, basiliximab is the most commonly used agent for induction, followed by thymoglobulin.[64]

Maintenance

The standard maintenance immunosuppression regimen immediately after heart transplantation is triple therapy with a calcineurin inhibitor (usually tacrolimus), mycophenolate mofetil, and prednisone. While most patients will remain on tacolimus and mycophenolate long-term, prednisone is frequently tapered off by the end of the first post-transplant year.[64] If patients develop chronic rejection or renal injury from calcineurin inhibitors, mTOR inhibitor can be substituted either for tacolimus or mycophenolate as long-term immunosuppression.[65] To date, newer agents like belatacept have not been studied after heart transplantation.

PATHOPHYSIOLOGY OF REJECTION

Rejection of a transplanted organ can take place at any time following surgery. Rejection can be differentiated based on time from transplantation (eg, early vs late) and/or by the pathophysiologic processes that underlie the rejection. Classically, this would include hyperacute rejection, acute, or chronic rejection, with further immunologic classification as either cellular rejection, antibody-mediated rejection, or some combination thereof.

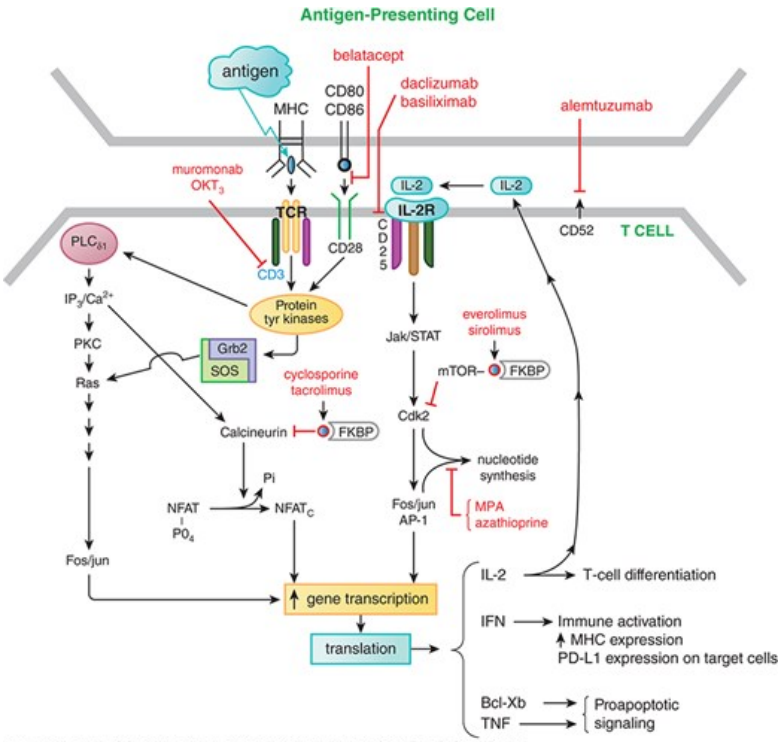
General Concepts

Rejection is primarily mediated by activation of alloreactive lymphocytes (Fig. 109-2). T-cells and antigen-presenting cells (APC) such as B-cells, macrophages, and dendritic cells coordinate to create a toxic, inflammatory milieu targeting non-self tissue (eg, the transplanted organ).[66]

FIGURE 109-2

T-cell activation and sites of action of immunosuppressive agents. The TCR recognizes antigens bound to the MHC. A costimulatory signal is required for T-cell activation: the CD80/CD86-CD28 interaction from the APC to the T cell. Activation leads to IL-2 production (in a positive-feedback loop) and a host of other events, some of which are bracketed in the lower right-hand corner. Numerous agents are available to suppress T-cell activation. Belatacept blocks the CD80/CD86-CD28 interaction. Cyclosporine and tacrolimus bind to immunophilins (cyclophilin and FKBP, respectively), forming a complex that inhibits the phosphatase calcineurin and the calcineurin-catalyzed dephosphorylation that permits translocation of NFAT into the nucleus. NFAT is required for transcription of IL-2 and other growth and differentiation–associated cytokines (lymphokines). Sirolimus (rapamycin)

and everolimus work downstream of the IL-2R, binding to FKBP; the FKBP-sirolimus complex binds to and inhibits the mTOR, a kinase involved in cell cycle progression (proliferation). MMF and azathioprine inhibit nucleic acid synthesis, thereby inhibiting T-cell proliferation. The antibody muromonab (OKT3) inhibits TCR function via interaction with its CD3 component. Daclizumab and basiliximab block IL-2 signaling by interacting with the alpha subunit of the IL-2R complex (CD25). Several antibodies can block the systemic effects of released TNF. Alemtuzumab, by binding to CD52, marks the cell for destruction, thereby depleting $CD52^+$ cells. (APC, antigen-presenting cell; FKBP, FK506-binding protein; IFN, interferon; IL-2R, interleukin 2 receptor; MHC, histocompatibility complex; mTOR, mammalian target of rapamycin; NFAT; nuclear factor of activated T lymphocytes; OKT3, muromonab CD3; PD-L1, programmed death ligand 1.) *(Adapted from Immunosuppressants and Tolerogens, Brunton LL, Hilal-Dandan R, Knollmann BC. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e; 2017.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Chromosome 6 contains an extremely polymorphic region of DNA known as the human leukocyte antigen (HLA) system, which encodes the blueprint for the expression of self-antigen on every nucleated cell in the body.[67] The first event that occurs in the complex sequence of organ rejection is the recognition of foreign, non-self molecules. This is facilitated primarily by APC that recognizes either class I (eg, HLA-A, -B, and -C) or class II (HLA-DR, -DP, and -DQ) antigens that are expressed throughout the allograft. Antigen-specific T-cell activation proceeds, leading to graft injury/destruction. The specifics of this immune cascade of organ rejection are discussed in Chapter e106.

Hyperacute Rejection

Hyperacute rejection occurs when pre-formed donor-specific antibodies are present in the recipient at the time of the transplant. These may be anti-HLA antibodies or anti-ABO antibodies between donor and recipient with incompatible blood group types. Due to the "primed" nature of this immune response, it can be evident within minutes of graft reperfusion. Tissue damage is mediated through antibody-dependent, cell-mediated cytotoxicity, or through activation of the complement cascade. The ischemic damage to the microvasculature rapidly results in tissue necrosis and ultimately graft failure.[68]

Hyperacute rejection has become uncommon in solid-organ transplantation with the advent and subsequent advancement of crossmatching. A positive lymphocytotoxic crossmatch presents a serious risk for graft failure even if hyperacute rejection does not occur.[69] A negative crossmatch does not entirely rule out the possibility of hyperacute rejection because non-HLA antigens on the vascular endothelium can serve as targets of donor-specific antibodies.

Acute Cellular Rejection

Acute rejection is the most common form of allograft rejection, typically occurring in the first few months following transplantation, though it can occur at any time during the life of the allograft. With acute cellular rejection, alloreactive T-lymphocytes appear in the circulation and infiltrate the allograft through the vascular endothelium. Cytotoxic T-cells specifically target and damage functioning cells in the allograft. At the same time, local release of lymphokines attracts and stimulates macrophages to cause tissue damage through a delayed hypersensitivity-like mechanism. These immunologic and inflammatory events lead to nonspecific signs and symptoms that may include pain and tenderness over the graft site, fever, and lethargy. End-organ dysfunction is often evident, especially in patients with higher-grade ACR (Table 109-3). Strategies to reverse acute cellular rejection include the addition of an additional maintenance agent(s), bolus corticosteroids with a taper, and possibly lymphocyte-depleting therapy (Fig. 109-3).

TABLE 109-3

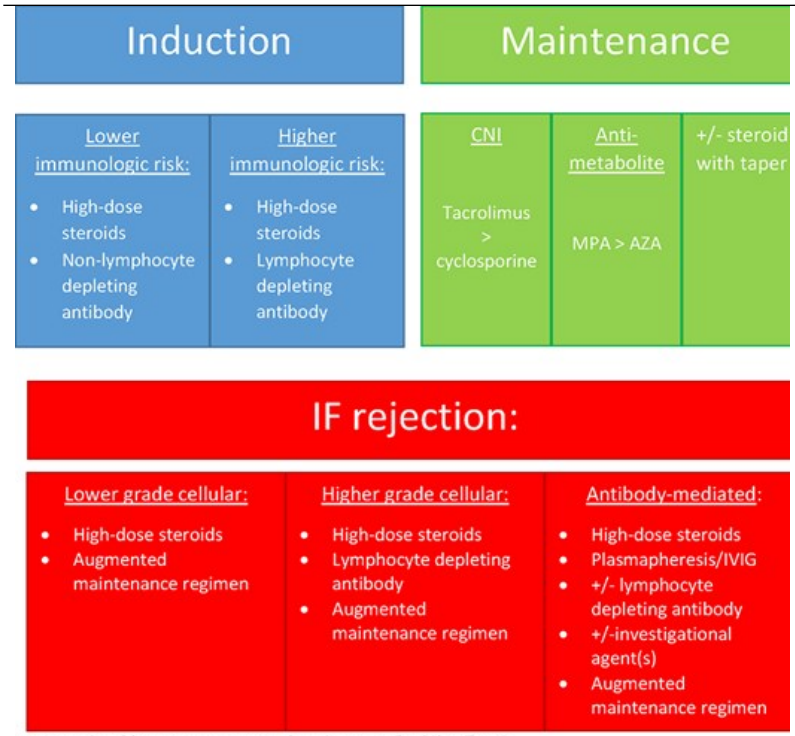
Acute Cellular Rejection After Transplant

	Percent of Patients with ≥1 Rejection Event Within the First Year Post-transplant	Signs/Symptoms of Rejection	Monitoring Strategies for Detecting Rejection
Kidney	7.1%	Elevated SCr, BUN, reduced UOP	Biopsy
Liver	12.3%	Elevated AST/ALT/Alkaline Phosphatase	Biopsy
Lung	16%	Reduced PFT, hypoxia, shortness of breath	PFT, bronchoscopy, biopsy
Heart	25.1%	Reduced ejection fraction, new dysrhythmia, overt heart failure	Right heart catheterization, echocardiogram, electrocardiogram, biopsy

SCr, serum creatinine; BUN, blood urea nitrogen; UOP, urine output; AST, aspartate transaminase; ALT, alanine transaminase; PFT, pulmonary function tests.

FIGURE 109-3

Representative immunosuppression regimen following solid-organ transplantation. (MPA, mycophenolic acid; AZA, azathioprine; IVIG, intravenous immune globulin.)



Antibody-Mediated Rejection

Antibody-mediated rejection (AMR), sometimes referred to as vascular or humoral rejection, is characterized by the presence of donor-specific antibodies directed against HLA antigens present on the allograft vascular endothelium. The antibodies activate complement, which leads to the formation of the membrane attack complex that directly damages the allograft tissue and further attracts inflammatory cells. The resultant damage is histologically distinct from cellular rejection and involves microvascular injury.[70] Definitive diagnosis of AMR is based on the presence of three clinical features: presence of donor-specific antibodies, immunofluorescence staining of complement deposits in the microvasculature, and evidence of allograft dysfunction.[71,72] Circulating immune complexes often precede humoral rejection. This form of rejection is less common than cellular rejection and often occurs in the first 3 months after transplantation.[71] An increased risk of humoral rejection is associated with female sex, elevated PRA, and a positive crossmatch.[72] Strategies to reverse humoral rejection may include plasmapheresis, often in combination with intravenous immunoglobulin, high-dose intravenous corticosteroids, lymphocyte-depleting agents, proteasome inhibitors, rituximab, and augmented background maintenance immunosuppression.

Chronic Rejection

Chronic rejection is a major cause of graft loss. It presents as a slow and indolent form of ACR, in which the humoral immune system and antibodies against the vascular endothelium appear to play a role. Persistent perivascular and interstitial inflammation is a common finding. As a result of the complex interaction of multiple drugs and diseases over time, it is difficult to delineate the true nature of chronic rejection. While chronic rejection of the kidney, liver, or lung allograft is generally not amenable to drug therapy, 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase inhibitors are given to all heart transplant recipients to decrease the incidence of chronic rejection and prolong survival (Table 109-4).[73] The mTOR inhibitors sirolimus and everolimus may also decrease the incidence and slow progression of cardiac allograft vasculopathy; however, these agents are hampered by side effects and cannot be used in the early post-transplant setting (Table 109-4).[73]

TABLE 109-4

Strategies for Preventing Cardiac Allograft Vasculopathy (CAV)

Drug Class	Drugs	Dose	Timing of Initiation
Statins	Pravastatin Simvastatin Atorvastatin Rosuvastatin	20-40 mg daily 5-20 mg daily 10-40 mg daily 5-20 mg daily	Prior to hospital discharge
mTOR inhibitors	Everolimus Sirolimus	0.75 mg twice daily 1-2 mg daily	Not recommended to initiate within 6 months of transplant due to impaired wound healing. However, greatest benefit is realized if started within 1-2 years
Glycemic control	Insulin, other anti-hyperglycemic agents	Titrate to euglycenmia	Immediately post-transplant
Prevent ACR[a]	Tacrolimus Cyclosporine	Titrate to center-specific trough values	Immediately post-transplant
Prevent CMV infection[b]	Valganciclovir	900 mg daily (adjusted for kidney function)	Immediately post-transplant

ACR, acute cellular rejection; CMV, cytomegalovirus.

[a]Episodes of acute cellular rejection increase the subsequent risk of developing CAV.

[b]CMV infection has been linked to accelerated development of CAV. Prophylaxis with valganciclovir is only recommended in recipients at high risk of infection post-transplant.

IMMUNOSUPPRESSIVE MEDICATIONS FOR THE PREVENTION AND TREATMENT OF REJECTION

Rejection is both prevented and treated with combination drug therapy. A multi-drug approach is rational because immunotherapy agents have potentially synergistic mechanisms of action. Furthermore, the use of a multi-drug immunosuppression regimen may allow the use of lower doses of individual agents, thus reducing the severity of dose-related adverse effects (Fig. 109-3). Immunosuppression protocols tend to be medical center specific, and further tailoring of patient-specific regimens is standard practice.[61,74,75]

Depleting Antibody Therapies

Anti-thymocyte Globulin (ATG)

Two ATG formulations are available in the United States: ATG (Atgam, Pfizer, New York, NY), an equine polyclonal antibody, and RATG (Thymoglobulin, Genzyme, Cambridge, MA), a rabbit polyclonal antibody. The rabbit preparation is less immunogenic and hence has improved tolerability over the equine preparation.

Pharmacology/Mechanism of Action

Because of their polyclonal antibody nature, both ATG and RATG exert their immunosuppressive effect by binding to a wide array of lymphocyte receptors such as CD2, CD3, CD4, CD8, CD25, and CD45. Binding of ATG or RATG to the various receptors results in complement-mediated lysis and subsequent lymphocyte depletion. While T cells are the major lymphocytic target for the compounds, other blood cell components such as B cells and other leukocytes are also affected (see Fig. 109-2).

Pharmacokinetics

ATG is poorly distributed into lymphoid tissue and binds primarily to circulating lymphocytes, granulocytes, and platelets. The terminal half-life of ATG is 5.7 days. RATG has a volume of distribution of 0.12 L/kg, and its terminal half-life in kidney transplant recipients is significantly longer than ATG at 30 days.[76] Peak plasma concentrations are reached after 5 to 7 days of ATG or RATG infusions.

Efficacy

ATG and RATG are used for the treatment of acute allograft rejection or as induction therapy to prevent acute rejection.[77] When compared head-to-head in kidney transplant recipients, RATG resulted in less frequent and less severe acute rejection episodes, fewer serious adverse events and was superior with respect to the composite endpoint including freedom from death, graft loss, or rejection.[78] RATG received regulatory approval as induction therapy in kidney transplantation.[79] As such, RATG is both preferred over ATG for induction and treatment of rejection in solid-organ transplant recipients.

Use of RATG in liver transplantation as part of a steroid avoidance protocol is associated with similar rates of patient and graft survival and acute rejection compared with dual or triple therapy.[34] In kidney transplant, RATG is associated with improved graft survival at 5 years as compared with equine ATG. Quadruple-drug therapy results in similar rates of patient and graft survival in heart transplant recipients, with a lower rate of acute rejection at 1 year compared with triple-drug therapy. Outcomes associated with RATG in lung transplantation have not consistently demonstrated favorable outcomes related to acute rejection or patient and graft survival.[80,81]

Adverse Effects

Most adverse effects reported with ATG and RATG are related to the lack of specificity for lymphocytes. Dose-limiting myelosuppression (leukopenia, anemia, and thrombocytopenia) occurs frequently. Other adverse effects include anaphylaxis, hypotension, hypertension, tachycardia, dyspnea, urticaria, and rash. Serum sickness is seen more frequently with ATG than with RATG. Nephrotoxicity is rare in the absence of serum sickness. Infusion-related febrile reactions are common; therefore, all patients should be pre-medicated with acetaminophen, diphenhydramine, and corticosteroids. Finally, as with any immunosuppressive agent, ATG and RATG are associated with an increased risk of infections—particularly viral infections—and malignancy.

Drug-Drug and Drug-Food Interactions

There are no known drug or food interactions with ATG or RATG.

Dosing and Administration

ATG doses range from 10 to 30 mg/kg/day as a single dose for 7 to 14 days. A skin test (test dose) is required prior to administration of the initial dose of ATG. RATG is a more potent compound and is administered at doses of 1 to 1.5 mg/kg/day as a single daily dose for 7 to 14 days for acute rejection or for 3 to 10 days for induction of immunosuppression. ATG and RATG should both be administered through a central line or through a high-flow vein with an in-line 0.22-micron filter over at least 4 hours to minimize phlebitis and thrombosis.[76] Heparin and hydrocortisone are commonly added to the

infusion to minimize phlebitis and thrombosis.[76]

Alemtuzumab

Alemtuzumab is approved for use in B-cell chronic lymphocytic leukemia.[82] However, its effects on depleting both T and B lymphocytes make it useful in solid-organ transplants. While alemtuzumab is not FDA-approved for solid-organ transplantation, it is widely recognized as a viable therapeutic option for induction or treatment of acute rejection. In 2012, commercial distribution of alemtuzumab ceased for transplantation and leukemia, requiring centers to enroll in a distribution program for ongoing medication access.

Pharmacology/Mechanism of Action

Alemtuzumab is a humanized monoclonal antibody against the CD52 surface antigen found on both T and B lymphocytes, as well as macrophages, monocytes, eosinophils, and natural killer cells. When alemtuzumab binds to the CD52 surface antigen, antibody-dependent lysis occurs, which removes both T and B lymphocytes from the blood, bone marrow, and organs, resulting in complete lymphocyte depletion.[82]

Pharmacokinetics

The pharmacokinetics of alemtuzumab in solid-organ transplantation patients have not been investigated. In patients with B-cell chronic lymphocytic leukemia, the volume of distribution of alemtuzumab after repeated dosing is 0.18 L/kg. The mean half-life after the first 30 mg dose is 11 hours, but increases to 6 days after 12 weeks of therapy. The extrapolation of these pharmacokinetic data to solid-organ transplantation is difficult because of the differences in dosing strategies used for the FDA indication. One or two doses of alemtuzumab result in complete and prolonged lymphocyte depletion. Following administration, B lymphocyte counts return to normal within 3 to 12 months. T lymphocytes, however, remain depressed for as long as 3 years following administration.[82,83]

Efficacy

Alemtuzumab is effective as induction therapy for the prevention of acute rejection in kidney, liver, heart, pancreas, intestinal, and lung transplants.[84] Additionally, alemtuzumab has been used to successfully treat acute rejection following transplantation and is effective for corticosteroid- and antibody-resistant rejection.[72]

Adverse Effects

Adverse effects of alemtuzumab are primarily infusion-related, hematologic, and infectious. Because alemtuzumab causes complete lymphocyte depletion and associated cytokine release, infusion-related reactions include rigors, hypotension, fever, shortness of breath, bronchospasms, and chills. The potential for developing these reactions can be reduced by administering pre-medications such as acetaminophen, corticosteroids, and diphenhydramine or by administering smaller doses and escalating the dose gradually. Subcutaneous administration may also reduce the incidence of infusion reactions.[85] Hematologic effects include pancytopenia, neutropenia, thrombocytopenia, and lymphopenia.

Drug-Drug and Drug-Food Interactions

No drug or food interactions have been noted with alemtuzumab.

Dosing and Administration

Several dosing regimens have been proposed for alemtuzumab in solid-organ transplantation. The most common dosing strategy is 30 mg administered intravenously or subcutaneously as a single dose; some centers administer a second dose 1 to 5 days after transplantation. Other dosing strategies assessed include 0.3 mg/kg/dose, as a single- or multiple-dose regimen, and, finally, two 20-mg doses given on the day of transplantation and the first postoperative day.[82]

Non-Depleting Antibody Therapy

Basiliximab

Basiliximab, a chimeric monoclonal antibody (25% murine) is the only available IL-2 receptor antagonist currently marketed in the United States. It is approved for use in kidney transplantation but is also extensively used in other organ transplants as well.[86]

Pharmacology/Mechanism of Action

Basiliximab exerts its immunosuppressive effect by specifically binding with high affinity to the α-chain (CD25) on the surface of activated T lymphocytes (see Fig. 109-2). Binding of basiliximab to the IL-2 receptor prevents IL-2-mediated activation and proliferation of T cells, a critical step in clonal expansion of T cells and the development of allograft rejection. Saturation of the IL-2 receptor occurs rapidly and confers an immunosuppressive effect that lasts for 4 to 6 weeks after administration.[86]

Pharmacokinetics

Most of the pharmacokinetic data available for basiliximab was derived following administration to kidney transplant recipients. Caution must be used when extrapolating this information to other transplant recipients. The volume of distribution is approximately 8 L, and it has a half-life of approximately 7 days. Clearance is increased in patients who have received a liver transplant, and it may be necessary in patients with greater than 10 L of ascites to receive an additional dose of basiliximab on postoperative day 8.[87]

Efficacy

Basiliximab is approved for use in kidney transplantation in combination with cyclosporine and corticosteroids, although induction therapy has also been evaluated in liver, lung, and heart transplant recipients. Use of basiliximab in liver transplant recipients has been increasing as a means of delaying CNI initiation in the setting of acute kidney injury.[32,33] A meta-analysis of basiliximab efficacy in kidney transplantation concluded that IL-2 receptor antagonists reduced the risk of rejection with no increases in graft loss, infectious complications, malignancy, or death.[86] Similar results were seen in liver transplant patients.[88]

IL-2 receptor antagonists offer a reasonable addition to calcineurin inhibitor—or corticosteroid-sparing protocols. While CNI therapy cannot be completely avoided in most cases, IL-2 receptor antagonists allow for delayed use or reduced doses of CNIs, thus minimizing the risk of nephrotoxicity in the early post-transplantation period.[33]

Adverse Effects

Relatively few adverse effects have been observed with basiliximab. In contrast to lymphocyte-depleting agents, basiliximab is not associated with infusion-related reactions. However, since the marketing of basiliximab, an increased number of hypersensitivity reactions have been reported. Development of anti-idiotypic antibodies to the murine portion occurs rarely.[88] There appears to be no increased risk of malignancy.

Drug-Drug and Drug-Food Interactions

While cyclosporine and tacrolimus serum concentrations may increase in patients receiving concomitant basiliximab therapy, this interaction is not considered clinically.[86]

Dosing and Administration

Basiliximab is usually administered as two 20-mg intravenous doses, intraoperatively and again on postoperative day 4. Basiliximab is compatible with both 0.9% sodium chloride and 5% dextrose and can be administered either centrally or peripherally over 20 to 30 minutes in a volume of 50 mL.

Other Antibody Therapy

Immune Globulin

Immune globulin (more commonly intravenous immune globulin; IVIG) preparations are derived from human plasma and contain a mixture of antibodies that exert immunomodulatory effects. IVIG is often used prophylactically in solid-organ transplant recipients who are at particularly high risk for antibody-mediated rejection due to the presence of pre-formed DSA at the time of transplant surgery. IVIG may also be used for a variety of other post-transplant complications, including in the management of both cellular and antibody-mediated rejection, hypogammaglobulinemia, and many others that are beyond the scope of this text.

Pharmacology/Mechanism of Action

IVIG is thought to exert its immunomodulatory properties via a number of mechanisms, including inducing B-cell apoptosis and inhibition of complement.[72]

Pharmacokinetics

IVIG has a small volume of distribution (0.05-0.13 L/kg) and upon administration, immune globulin remains primarily in the intravascular compartment. The half-life varies by IVIG preparation but is generally between 14 and 28 days.[89]

Efficacy

When administered to sensitized patients awaiting kidney transplantation, IVIG results in reductions in circulating DSA.[90] Pre-transplant IVIG administration (in combination with plasmapheresis) that achieves desensitization may yield a mortality benefit in kidney transplant recipients owing to dialysis liberation.[91] IVIG leads to similar outcomes compared to anti-CD3 monoclonal antibody (OKT3) in patients being treated for steroid-resistant rejection.[92] IVIG is also often used in the setting of chronic antibody-mediated rejection, though supporting evidence for this practice is lacking.[93]

Adverse Effects

IVIG infusions can be complicated by reactions that include rash, chills, headaches, shortness of breath, or hypotension. For this reason, pre-medications are routinely administered. IVIG has also been known to rarely cause acute kidney injury (more frequently associated with sucrose-containing formulations due to osmotic diuresis), hemolysis, aseptic meningitis, and thromboembolism.[72]

Drug-Drug and Drug-Food Interactions

There are no known drug or food interactions with IVIG.

Dosing and Administration

IVIG doses range from 0.1 to 2 g/kg as either a single dose or doses that are administered sequentially, depending on the indication for use. IVIG infusions should generally begin at slower infusion rates to assess patient tolerability before up-titrating. If IVIG is being administered on the same day as plasmapheresis, then it should be administered after because immune globulin is removed by pheresis.

Maintenance Agents

The goal of maintenance immunosuppression is to prevent rejection while minimizing drug-related toxicity. As patients progress through the post-transplant course, the risk of acute rejection decreases and the need for pharmacologic immunosuppression is lessened. With few exceptions, maintenance immunosuppression can never be withdrawn following transplantation and thus one or more agents are required lifelong.

Calcineurin Inhibitors

Cyclosporine and tacrolimus are the two calcineurin inhibitors (CNIs) currently used for most solid-organ transplant recipients. More than 90% of transplant recipients receive tacrolimus as part of their immunosuppressive regimen.[94]

Pharmacology/Mechanism of Action

Calcineurin inhibitors block T-cell proliferation by inhibiting the production of IL-2 and other cytokines by T cells (see Fig. 109-2). Cyclosporine and tacrolimus bind to unique cytoplasmic immunophilins: cyclophilin and FK-binding protein-12 (FKBP12), respectively. The drug-immunophilin complex inhibits the action of calcineurin, an enzyme that activates the nuclear factor of activated T cells, which is, in turn, responsible for the transcription of several key cytokines necessary for T-cell activity, including IL-2. IL-2 is a potent T-cell growth factor and ultimately is responsible for activation and clonal expansion.

Pharmacokinetics

The calcineurin inhibitors are highly lipophilic compounds, with variable but generally low bioavailability of approximately 30% (range: 5%-60%). Unlike tacrolimus, cyclosporine depends on bile for intestinal absorption, which further increases inter- and intra-patient variability.

Because of the high variability in absorption of cyclosporine a microemulsion formulation was developed. Both forms are available commercially in the United States and are referred to as “cyclosporine, USP,” and “cyclosporine, USP [MODIFIED].” The two formulations are not bioequivalent and should not be used interchangeably. The modified formulation is self-emulsifying and forms a microemulsion spontaneously with aqueous fluids in the gastrointestinal tract, making it less dependent on bile for absorption. This translates into a greater rate and extent of absorption and decreased intra-individual variability in pharmacokinetic parameters. The relative bioavailability of the microemulsion formulation is 60%, and peak concentrations are reached within 1.5 to 2 hours after oral administration. Tacrolimus, on the other hand, has a more predictable absorption pattern, reaching peak concentrations within 1 to 3 hours with bioavailability of approximately 20%.[95]

Following oral absorption, both cyclosporine and tacrolimus are highly protein bound. Ninety percent of cyclosporine is bound to lipoproteins in the blood while 99% of tacrolimus is bound primarily to plasma proteins, including albumin and α_1-acid glycoprotein, and red blood cells. Cyclosporine is distributed widely into tissue and body fluids, resulting in a large and variable volume of distribution, ranging from 3 to 5 L/kg. Because of the high concentration of FKBP12 that is found in red blood cells, tacrolimus is distributed primarily in the vasculature, with a volume of distribution of 0.8 to 1.9 L/kg. Both drugs are extensively metabolized by cytochrome P450 3A4 (CYP3A4) in both the gut and the liver, which accounts for their numerous drug interactions that are highlighted in Table 109-5.[83,84,95,96] Cyclosporine and tacrolimus are both excreted primarily in the feces.

TABLE 109-5

The Impact of Concomitant Medications on Immunosuppressive Concentrations

Medications	TAC	CSA	MPA	mTOR Inhibitors
Anti-Infectives				
Clotrimazole	↑	↑		↑
Fluconazole	↑	↑		↑
Ketoconazole	↑	↑		↑
Voriconazole	↑	↑		↑
Itraconazole	↑	↑		↑
Posaconazole	↑	↑		↑
Erythromycin	↑	↑		↑

Clarithromycin	↑	↑		↑
Azithromycin	↑	↑		↑
Levofloxacin	↑	↑		
Metronidazole			↓	
Selective gut decontamination			↓	
Nafcillin	↓	↓	↓	↓
Rifampin	↓	↓	↓	↓
Lopinavir/Ritonavir	↑	↑		
Saquinavir				
Efavirenz	↓	↓		
Glecaprevir/pibrentasvir	↑	↑		↑
Letermovir	↑	↑		↑
Cobicistat	↑	↑		↑
Cardiovascular				
Verapamil	↑	↑		↑
Diltiazem	↑	↑		↑
CNS				
Carbamazepine	↓	↓		↓
Phenytoin	↓	↓		↓
Phenobarbital	↓	↓		↓
Immunosuppressants				

Cyclosporine			↓	↑
Tacrolimus				
Sirolimus		↑		
Everolimus		↑		
Mycophenolic acid		↓		

Efficacy

Both cyclosporine and tacrolimus are currently approved for prophylaxis of organ rejection in kidney, liver, and heart transplantation. They are both used as primary immunosuppression in lung transplant recipients despite not being approved for this purpose. The microemulsion formulation of cyclosporine has demonstrated equivalent or superior efficacy in kidney, liver, and heart transplantation recipients relative to the non-modified formulation. Tacrolimus and cyclosporine demonstrate equivalent efficacy as primary immunosuppression in regard to overall patient mortality, but tacrolimus is the preferred CNI owing to its superiority in preventing acute rejection.[97]

Adverse Effects

The adverse effects of immunosuppressants are presented in Table 109-6. The nephrotoxic potential of both drugs is equal and is often related to the dose and duration of exposure. Neurotoxicity typically manifests as tremors, headache, and peripheral neuropathy; occasionally, however, seizures have been observed. Tacrolimus may be associated with an increased occurrence of neurologic complications compared with cyclosporine.[97]

TABLE 109-6

Comparison of Common Adverse Effects of Maintenance Immunosuppressants

System/Adverse Effect	AZA	MPA	CNI	Steroids	mTOR	Bela
Neurologic						
Headache			X			
Tremors			X			
Seizures			X			
Mood changes				X		
Cardiovascular						
Hypertension			X	X		

Hyperlipidemia			X	X	X	
Peripheral edema						X
Gastrointestinal						
Nausea	X	X	X	X		
Diarrhea		X	X			X
Vomiting	X					
Bleeding				X		
Hepatotoxicity	X		X			
Renal						
Nephrotoxicity			X		X	
Hyperkalemia			X			
Hypomagnesemia			X			
Urinary tract infection						X
Hematologic						
Anemia						X
Leukocytosis						
Leukopenia	X	X			X	
Neutropenia						X
Thrombocytopenia	X	X			X	
Cosmetic						
Acne				X		

Alopecia			TAC			
Gingival hyperplasia			CSA			
Hirsutism			CSA			
Weight gain				X		
Endocrine						
Hyperglycemia			X	X		
Osteoporosis				X		

AZA, azathioprine; Bela, belatacept; CNI, calcineurin inhibitor; CSA, cyclosporine; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin inhibitor; TAC, tacrolimus.

Cyclosporine has a greater propensity to cause hypertension and hyperlipidemia compared with tacrolimus.[98,99] Conversely, hyperglycemia is more common with tacrolimus than with cyclosporine but is often reversible when doses of tacrolimus are reduced.[98] Cyclosporine is associated with cosmetic effects, such as hirsutism and gingival hyperplasia, which may be managed by converting from cyclosporine to tacrolimus. Tacrolimus, in contrast, may cause alopecia, which is usually self-limiting and reversible.

Calcineurin Inhibitor-Associated Nephrotoxicity

Two types of nephrotoxicity can occur with calcineurin inhibitors. Acute nephrotoxicity is seen early and is dose-dependent and reversible, but chronic nephropathy is more problematic. Clinical manifestations of calcineurin inhibitor nephrotoxicity include elevated serum creatinine and blood urea nitrogen concentrations, hyperkalemia, hyperuricemia, proteinuria, and a decreased fractional excretion of sodium. Calcineurin inhibitor nephrotoxicity is the leading cause of impaired kidney function following a non-renal solid-organ transplant, a complication associated with reduced overall patient survival.[100]

The predominant mechanism for calcineurin inhibitor nephrotoxicity is renal vasoconstriction, primarily of the afferent arteriole, resulting in increased renal vascular resistance, decreased renal blood flow by up to 40%, reduced glomerular filtration rate by up to 30%, and increased proximal tubular sodium reabsorption with a reduction in urinary sodium and potassium excretion. A number of other mechanisms have been implicated, including changes in the renin–angiotensin–aldosterone system, prostaglandin synthesis, nitrous oxide production, sympathetic nervous system activation, and calcium handling.[101]

Several approaches have been proposed to reduce calcineurin inhibitor nephrotoxicity, including delaying administration immediately postoperatively in patients at high-risk for nephrotoxicity (using alternative induction protocols including an IL-2 receptor antagonist or antilymphocyte globulin), reducing the calcineurin inhibitor dosage to target lower blood concentrations (if feasible clinically), and avoiding other nephrotoxins (eg, aminoglycosides, amphotericin B, angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory agents) when possible.[101,102] No proven therapies consistently prevent or reverse the nephrotoxic effects of calcineurin inhibitors.

In patients who have received a kidney transplant, it is often difficult to differentiate calcineurin inhibitor nephrotoxicity from kidney allograft rejection. Because the clinical features of acute kidney allograft rejection and calcineurin inhibitor nephrotoxicity overlap considerably, a kidney biopsy is often necessary to differentiate the two (Table 109-7). However, differentiating between chronic kidney allograft rejection and calcineurin inhibitor nephrotoxicity may be more difficult because in addition to clinical signs and symptoms, biopsy findings may also be similar.

TABLE 109-7

Differential Diagnosis of Acute Rejection and Cyclosporine or Tacrolimus Nephrotoxicity

	Nephrotoxicity in Renal Transplant Recipients	
	Acute Rejection	**CSA or TAC Nephrotoxicity**
History	Often <4 weeks postoperatively	Often >6 weeks postoperatively
Clinical presentation	Fever	Afebrile
	Hypertension	Hypertension
	Weight gain	Graft nontender
	Graft swelling/tenderness	Good urine output
	Decreased daily urine volume	
Laboratory biopsy	Rapid rise in SCr	Gradual rise in SCr
	Normal or sub-therapeutic CSA or TAC concentration	Elevated CSA or TAC concentration, especially over long periods of time
	Interstitial lymphocytic infiltrates, peritubular capillaritis, +/- new donor-specific antibodies	Interstitial fibrosis, tubular atrophy, glomerular thrombosis, arterial inflammation

SCr, serum creatinine; CSA, cyclosporine; TAC, tacrolimus.

Drug-Drug and Drug-Food Interactions

Drug interactions occur frequently with the calcineurin inhibitors because they are substrates for CYP3A4 and P-glycoprotein.[83,84,96] The most commonly administered drugs that are known to alter cyclosporine and tacrolimus concentrations are highlighted in Table 109-5. Inhibitors of CYP3A4, such as –azole antifungals, protease inhibitors, diltiazem or erythromycin, can increase drug concentrations, whereas drugs that induce CYP3A4 activity, such as phenytoin or rifampin, can decrease drug concentrations.[96]

Cyclosporine, and to a lesser extent, tacrolimus, are inhibitors of CYP3A4 and P-glycoprotein.[95,103] The inhibitory effects of cyclosporine and tacrolimus on CYP3A4 can be seen with weaker substrates, such as the HMG-CoA reductase inhibitors (“statins”). Concomitant administration of a calcineurin inhibitor with an HMG-CoA reductase inhibitor may result in an increase in the HMG-CoA reductase inhibitor concentrations (particularly those metabolized by CYP3A4), which increases the risk of HMG-CoA reductase inhibitor adverse effects, most notably myopathy.[104] Patients should be monitored for clinical signs of myopathy when receiving HMG-CoA reductase inhibitors in combination with cyclosporine and tacrolimus. The interaction appears to be more pronounced between cyclosporine and HMG-CoA reductase inhibitors due to inhibition of organic anion-transporter proteins (OATP) by cyclosporine.[105]

Consistency in the administration of the calcineurin inhibitors with regard to meals and food intake is important to sustain an effective concentration–time profile. High-fat meals can enhance both plasma clearance and the volume of distribution of cyclosporine by more than 60%.[106] Food reduces the

rate and extent of tacrolimus absorption, and a high-fat meal may further delay gastric emptying and reduce the maximum achieved serum concentration (C_{max}) and the area under the concentration–time curve (AUC).[95] Furocoumarins such as quercetin, naringin, and bergamottin—found in grapefruit juice—are potent inhibitors of CYP3A4 and may increase both cyclosporine and tacrolimus concentrations. The AUC and C_{max} of cyclosporine may be increased by more than 55% and 35%, respectively.

Dosing and Administration

Initial oral cyclosporine doses range from 6 to 10 mg/kg/day administered in divided doses every 12 hours. Oral tacrolimus doses usually are in the range of 0.1 to 0.3 mg/kg/day in divided doses administered every 12 hours. An extended-release tablet formulation of tacrolimus (Envarsus XR®) has greater bioavailability than the immediate-release formulation and thus a lower recommended daily starting dose (0.14 mg/kg/day).[107] Children often require higher doses to maintain therapeutic drug concentrations, up to 14 to 18 mg/kg/day for cyclosporine and 0.3 mg/kg/day for tacrolimus. Astagraf XL®, another extended-release tacrolimus formulation, and Envarsus XR® are not interchangeable. Astagraf XL® (or Advagraf®) is generally converted from standard tacrolimus formulations on a mg:mg basis, whereas Envarsus® XR has greater bioavailability than the immediate release tacrolimus and thus a 20% reduction in total daily dose is recommended.[95,107,108]

If oral administration is not possible, both CSA and TAC can be administered intravenously. Intravenous cyclosporine should be converted at approximately one-third of the total daily oral dosage since administration by this route avoids first-pass metabolism. The usual intravenous dose of cyclosporine is 0.5 to 2 mg/kg/day, given as a continuous infusion or as a single or twice-daily injection. Intravenous tacrolimus should be converted at approximately one-fourth of the total daily oral dosage, with doses ranging from 0.03 to 0.05 mg/kg/day, and must be administered by continuous infusion.

Therapeutic Drug Monitoring

Calcineurin inhibitor trough blood concentrations should be measured routinely to optimize therapy. Both drugs can be measured by radio immunoassay (RIA) or high-performance liquid chromatography (HPLC), which is recognized as the reference procedure.[106] Therapeutic target ranges are assay specific. The specific goal concentration for both drugs is dependent on transplant type, time after transplantation, and concomitant immunosuppression, among other factors. However, target tacrolimus trough concentrations early post-transplantation (ie, 0-3 months) are around 8 to 15 ng/mL (mcg/L; 9.9-18.6 nmol/L) and are reduced over time as clinically tolerated/feasible. Drug concentrations should be measured frequently (daily or three times per week) following initiation of the drug and during the stabilization period after transplantation. With time, blood concentrations can be measured less frequently.

Cyclosporine trough concentrations are poorly predictive of rejection but are the most commonly utilized strategy for therapeutic drug monitoring. In the early post-transplantation period, goal cyclosporine trough concentrations range from 250 to 350 ng/mL (mcg/L; 210-290 nmol/L) and are similarly reduced over time. Alternative strategies, including AUC and peak concentration determination, have been suggested to better correlate with rejection.[106] Limited sampling techniques using two to five blood samples within the first 4 hours after an oral dose have been used to determine AUC and values greater than 4,400 ng/mL/hr correlated with a reduction in rejection.[106,109] Cyclosporine peak concentration (C_{peak}) has also been found to correlate with rejection and toxicity. Some transplantation centers have adopted this strategy to manage cyclosporine concentrations because of the convenience and reduced cost associated with the measurement of a single blood concentration. The suggested therapeutic range for C_{peak} cyclosporine concentrations is 1,500 to 2,000 ng/mL (µg/L; 1,250-1,660 nmol/L) for the first few months after transplant and 700 to 900 ng/mL (µg/L; 580-750 nmol/L) after 6 to 12 months.[106]

Current therapeutic drug monitoring does not ensure complete avoidance of either toxicity or rejection. Intra-patient variability with tacrolimus has been associated with both graft rejection and development of *de novo* donor-specific antibodies. Other measures of CNI exposure such as time in therapeutic range (TTR), commonly employed to measure the adequacy of warfarin monitoring, are positively associated with superior outcomes in lung transplant recipients. Prospective implementation of these findings has not been employed to drive outcomes but may be an opportunity to identify patients at heightened risk for poor outcomes and modify their clinical monitoring.[109-111]

Corticosteroids

Corticosteroids have been used since the beginning of the modern transplantation era. Despite their many adverse events, they continue to be a cornerstone of immunosuppression regimens in many transplant centers.[94] The most commonly used corticosteroids are methylprednisolone and prednisone.

Pharmacology/Mechanism of Action

Corticosteroids block cytokine activation by binding to corticosteroid response elements, thereby inhibiting IL-1, IL-2, IL-3, IL-6, γ-interferon, and tumor necrosis factor-α synthesis. Additionally, corticosteroids interfere with cell migration, recognition, and cytotoxic effector mechanisms.[112]

Pharmacokinetics

Prednisone is converted to prednisolone, its active moiety, in the liver and has multiple effects on the immune system. Prednisone is rapidly absorbed from the GI tract, achieving peak concentrations in 1 to 3 hours in transplant recipients. Bioavailability is greater than 90%. In kidney transplant recipients, the pharmacokinetic half-life is short, 2 to 4 hours, but the pharmacodynamic effects extend beyond the time that concentrations are measurable, permitting daily administration.[112]

Efficacy

The efficacy of corticosteroids is irrefutable based on the decades of clinical experience. Systematic studies comparing corticosteroid-free immunosuppressive agent combinations with conventional therapy are difficult to perform because of the many of potential combinations that now exist. Nevertheless, corticosteroid-free immunosuppressive agent combinations with newer, more specific immunosuppressants hold promise and may be more commonly used in the future.[113]

Adverse Effects

Adverse effects of prednisone that occur in more than 10% of patients include increased appetite, insomnia, indigestion, and mood changes. Side effects that occur less often but which are seen with high doses or prolonged therapy include cataracts, hyperglycemia, hirsutism, bruising, acne, sodium and water retention, hypertension, bone growth suppression, and ulcerative esophagitis. The adverse effects of corticosteroids are summarized in Table 109-6.

Drug-Drug and Drug-Food Interactions

Barbiturates, phenytoin, and rifampin induce hepatic metabolism of prednisolone and thus may decrease the effectiveness of prednisone. Prednisone decreases the effectiveness of vaccines and toxoids.[112]

Dosing and Administration

An intravenous corticosteroid, commonly high-dose methylprednisolone (250-1,000 mg), is given at the time of most solid-organ transplant surgeries and over consecutive days for the treatment of acute rejection. The dose of methylprednisolone is tapered and usually discontinued when oral prednisone is initiated. Prednisone doses are tapered progressively over several weeks to months, as dictated by center-specific protocols. It is preferable to administer corticosteroids in the early morning to mimic the body's diurnal release of cortisol. Prednisone should be taken with food to minimize GI upset. Abrupt corticosteroid discontinuation is not generally recommendable; tapering should be gradual because of the risk for suppression of the hypothalamic–pituitary–adrenal axis. While conversion to alternate-day regimens or complete withdrawal of prednisone in patients with stable post-transplantation courses has been used with success in some transplantation centers, corticosteroids are often continued for the entire life of the functional graft.[112]

Antimetabolites

Antimetabolites have been used since the early days of transplantation because they prevent the proliferation of lymphocytes. Azathioprine, long considered a part of the "gold standard" regimen with cyclosporine and corticosteroids, has largely been supplanted by mycophenolic acid derivatives which are more specific in their effects on lymphocytes and have fewer side effects.

Mycophenolic Acid Derivatives

Two formulations of mycophenolic acid (MPA) are currently available in the United States: mycophenolate mofetil—the morpholinoethyl ester of MPA—and mycophenolate sodium, which is available as an enteric-coated formulation of the sodium salt of MPA.

Pharmacology/Mechanism of Action

The immunosuppressive effect of MPA is exerted through non-competitive binding to inosine monophosphate dehydrogenase (IMPDH), the key enzyme responsible for guanosine nucleotide synthesis via the de novo pathway. Inhibition of IMPDH results in decreased nucleotide synthesis and diminished DNA polymerase activity, ultimately reducing lymphocyte proliferation.[114] Although MPA inhibits both types of IMPDH: IMPDH I, expressed by all cells in the body, and IMPDH II, which is expressed only in T and B lymphocytes, it is more specific for IMPDH II.[114] T and B lymphocytes only use the de novo pathway for nucleotide synthesis (see Fig. 109-2), making MPA specific for these cells. Other cells within the body have a salvage pathway by which they can synthesize nucleotides, making them less susceptible to the actions of MPA and thereby reducing, but not eliminating, the potential for the hematologic adverse effects seen with azathioprine. In addition to decreasing lymphocyte proliferation, MPA may also downregulate the activation of lymphocytes.[115]

Pharmacokinetics

Because MPA is unstable in an acidic environment, mycophenolate mofetil acts as a prodrug that is readily absorbed from the GI tract, after which it is rapidly and completely converted to MPA by the liver. The enteric coating of mycophenolate sodium protects MPA from the acidic gastric pH and allows MPA to be released directly into the small intestine for absorption. The absolute bioavailability of mycophenolate mofetil and mycophenolate sodium is 94% and 72% of the active moiety, respectively. Peak concentrations of mycophenolate mofetil are reached within 1 to 2 hours following oral administration, while the enteric coating of mycophenolate sodium delays absorption and peak concentrations are not reached until 4 hours after administration.[115]

MPA is extensively bound (97%) to albumin and is eliminated by the kidney and also undergoes glucuronidation in the liver to an inactive glucuronide metabolite (MPAG) that is subsequently excreted in the bile and urine. Enterohepatic cycling of MPAG can lead to deconjugation, thereby recirculating MPA into the bloodstream. This can account for 10% to 60% of total MPA exposure and results in a second peak 6 to 12 hours after oral administration. The half-life of MPA is 18 hours.[115]

Efficacy

Mycophenolate mofetil is approved for use in kidney, liver, and heart transplantation and is recommended as a component of maintenance immunosuppression regimens for most all solid-organ transplant recipients.[61,75] Compared to azathioprine, mycophenolate treatment in patients receiving cyclosporine and corticosteroids leads to a significant improvement in patient and graft survival at 1 and 3 years.[115]

Mycophenolic acid derivatives are a key component of calcineurin inhibitor–sparing protocols. MPA monotherapy has been associated with an unacceptable rejection rate. Combination of MPA with sirolimus, on the other hand, resulted in improved kidney function with no change in acute rejection incidence or patient and graft survival.[115]

Adverse Effects

Unlike cyclosporine and tacrolimus, MPA is not associated with nephrotoxicity, neurotoxicity, or hypertension. The most common side effects are related to the GI tract, including nausea, vomiting, diarrhea, and abdominal pain (see Table 109-6), which occur with similar frequency during intravenous and oral therapy. Strategies to reduce GI symptoms are not well established. Changing formulation may or may not improve symptoms and it is clear that dose reduction and discontinuation increase the risk of rejections.[115] Mycophenolic acid also has hematologic effects, such as leukopenia and anemia, particularly with higher doses, and may be associated with the rare but serious adverse event of progressive multifocal leukoencephalopathy (PML).[115]

Drug-Drug and Drug-Food Interactions

Food has no effect on MPA AUC, but it delays the absorption and decreases MPA C_{max} by 40% and 33% when mycophenolate mofetil and mycophenolate sodium, respectively, are administered. Concomitant administration with aluminum- and magnesium-containing antacids decreases the AUC of MPA, though the significance of this interaction is not likely clinically relevant.[115] Administration of iron may produce similar results, but this has not been tested. Concomitant administration of mycophenolate mofetil with pantoprazole decreases MPA concentrations and systemic exposure in healthy volunteers. The same effect is not observed with mycophenolate sodium. Reduced MPA exposure does not impact graft outcomes in all patients.

Acyclovir, commonly used in kidney transplant recipients for the treatment and prevention of viral infections, competes with MPAG for renal tubular secretion. AUCs of both entities are increased during concomitant acyclovir and MPA administration. No pharmacokinetic interaction with other antiviral agents has been demonstrated; but, there is potential for additive pharmacodynamic effects such as bone marrow suppression.

Decreased MPA trough concentrations are observed when MPA is administered with cyclosporine compared with those achieved when MPA is given with tacrolimus or sirolimus.[115] This interaction is most likely a result of cyclosporine inhibition of multidrug-resistance-associated protein 2 (MRP2), which inhibits the enterohepatic recycling of MPAG, resulting in decreased MPA concentrations.[115] Cyclosporine decreases MPA concentrations by approximately 40% to 50% compared to tacrolimus.[83] To achieve equivalent MPA and MPAG serum concentrations, it may be necessary to administer higher doses of MPA with cyclosporine compared to tacrolimus. Antibiotics may also interfere with enterohepatic recycling of MPAG by decreasing bacterial-mediated de-glucuronidation in the colon.[115] MPA concentrations may also be reduced in the setting of concomitant corticosteroid administration, owing to the induction of glucuronidation caused by steroids.[116]

Dosing and Administration

Mycophenolate mofetil is currently available in both oral and intravenous formulations. Although intravenous administration of equal doses closely mimics oral administration, the two cannot be considered bioequivalent. Mycophenolate sodium is only available as an oral formulation. To optimize immunosuppression and minimize adverse effects, MPA is most commonly administered in two divided doses given every 12 hours. The total daily dose for kidney and liver transplants is typically 2 g/day for mycophenolate mofetil and 1.44 g/day for mycophenolate sodium. The total daily dose in heart transplant recipients is commonly 3 g/day, with a target trough concentration of greater than 1.5 µg/mL (mg/L; 4.7 µmol/L).[61] The recommended pediatric dose is 600 mg/m^2 for mycophenolate mofetil and 400 mg/m^2 for mycophenolate sodium, in two divided doses.

While therapeutic drug monitoring of MPA may be of value it remains controversial.[117-119] Plasma appears to be the most appropriate medium in which to measure MPA for therapeutic drug monitoring, due to the relationship between target plasma MPA concentrations and improved clinical outcomes in patients receiving concomitant CNIs and corticosteroids. For example, patients with trough MPA concentrations between 1.0 and 3.5 µg/mL (mg/L; 3.1-10.9 µmol/L) experience fewer complications. Unbound concentrations as opposed to total MPA concentrations may be the most relevant to measure, especially in patients with liver disease, hypoalbuminemia, and severe infection.[115] Trough concentrations may not be accurate in predicting total drug exposure during a 12-hour interval and thus AUC monitoring has been proposed as the most appropriate measure of MPA drug exposure to guide therapy.[115] Better outcomes are associated with MPA AUC concentrations of greater than 42.8 µg/mL (mg/L; 134 µmol/L) per hour (by HPLC), although a reference range of 30 to 60 µg/mL (mg/L; 94-188 µmol/L) has been proposed.[119] The correlation between MPA AUC values and adverse effects is low. The best means to evaluate MPA concentrations, the acceptable targets for each method, and the appropriate strategy to monitor MPA concentrations remain unclear.[119]

Azathioprine

Azathioprine, a prodrug for 6-mercaptopurine (6-MP), has been used as an immunosuppressant in combination with corticosteroids since the earliest days of the modern transplantation era. Its use has dramatically declined with the availability of newer immunosuppressants, but it remains an option for patients intolerant of other medications.[61,75]

Pharmacology/Mechanism of Action

Azathioprine is an inactive compound that is converted rapidly to 6-MP in the blood and is subsequently metabolized by three different enzymes.

Xanthine oxidase, found in the liver and GI tract, converts 6-MP to the inactive final end product, 6-thiouric acid. Thiopurine *S*-methyltransferase (TPMT), found in hematopoietic tissues and red blood cells, methylates 6-MP to an inactive metabolite, 6-methylmercaptopurine. Finally, hypoxanthine-guanine phosphoribosyltransferase is the first step responsible for converting 6-MP to 6-thioguanine nucleotides (6-TGNs), the active metabolites, which are incorporated into nucleic acids, ultimately disrupting both the salvage and de novo pathways of DNA, RNA, and protein synthesis. This process is toxic to the cell and renders the cell unable to proliferate (see Fig. 109-2). Eventually, 6-TGNs are catabolized by xanthine oxidase and thiopurine *S*-methyltransferase to inactive products.[118]

Pharmacokinetics

Oral bioavailability of azathioprine is approximately 40%. Metabolism of 6-MP is primarily by xanthine oxidase to inactive metabolites, which are excreted by the kidneys. The half-life of azathioprine is short, approximately 12 minutes. The half-life of 6-MP is longer, ranging from 0.7 to 3 hours. However, it is the activity of the 6-TGNs that determines the pharmacodynamic half-life of the drug which has been estimated to be 9 days.[120]

Adverse Effects

Dose-limiting adverse effects of azathioprine are often hematologic (see Table 109-6). Leukopenia, anemia, and thrombocytopenia can occur within the first few weeks of therapy and can be managed by dose reduction or discontinuation of azathioprine. Other common adverse effects include nausea and vomiting, which can be minimized by taking azathioprine with food. Alopecia, hepatotoxicity, and pancreatitis are less common adverse effects of azathioprine and are reversible on dose reduction or discontinuation. Activity of TPMT can affect the occurrence of adverse effects with azathioprine. Approximately 10% of the population has intermediate TPMT activity and 0.3% has low activity of the enzyme. In both scenarios, the incidence of leukopenia and hepatotoxicity is increased.

Drug-Drug and Drug-Food Interactions

The xanthine oxidase inhibitors allopurinol and febuxostat increase azathioprine and 6-MP concentrations by as much as fourfold.[120] The metabolic pathways shift to favor the production of 6-TGNs, which ultimately results in increased bone marrow suppression and pancytopenia. Doses of azathioprine should be reduced by at least 50% to 75% when allopurinol is added to a patient's drug regimen.

Dosing and Administration

Usual initial doses of azathioprine range from 1 to 3 mg/kg/day orally. An intravenous formulation exists but is variably available and thus infrequently used in clinical practice.

Mammalian Target of Rapamycin (mTOR) Inhibitors

Two mTOR inhibitors have been approved in the United States for use in transplantation. Sirolimus, also known as rapamycin, is an immunosuppressive macrolide antibiotic that is structurally similar to tacrolimus, and is effective in reducing the risk of acute rejection. Everolimus, a synthetic derivative of sirolimus that was approved in the United States in 2009, was developed to improve upon the pharmacokinetics of sirolimus.

Pharmacology/Mechanism of Action

Sirolimus and everolimus both bind to FKBP12, forming a complex that binds to mTOR, which inhibits the body's response to cytokines (see Fig. 109-2). IL-2 stimulates mTOR to activate kinases that ultimately advance the cell cycle from G1 to the S phase. Thus, these drugs reduce T-cell proliferation by inhibiting the cellular response to IL-2 and progression of the cell cycle.[121,122]

Pharmacokinetics

Bioavailability after oral administration is low for both, only 14% to 20%, with peak concentrations being reached within 1 to 2 hours.[121,122] Both have large volumes of distribution, 5.6 to 16.7 L/kg for sirolimus and between 128 and 529 L for everolimus. Both are metabolized primarily by CYP3A4 in the gut and the liver. Likewise, both are also substrates for P-glycoprotein. The half-life for sirolimus is 60 hours but can be as long as 110 hours in patients with liver dysfunction, while that of everolimus is much shorter (18-35 hours).[121,122]

Efficacy

Sirolimus is approved for the prevention of rejection in kidney transplant recipients when given in combination with corticosteroids and cyclosporine, or after withdrawal of cyclosporine in patients with low-to-moderate immunologic risk. Sirolimus is also effective in combination with tacrolimus or mycophenolate in kidney transplants, with patient survival rates greater than 99% and graft survival rates greater than 96%.[112] Combination therapy with sirolimus and mycophenolate can be used to avoid the use of calcineurin inhibitors and decrease the risk of nephrotoxicity. Everolimus is approved for use in both kidney and liver transplantation. In kidney transplant recipients, it was evaluated in combination with basiliximab, cyclosporine, and corticosteroids, whereas in liver transplant recipients, it was initiated at least 30 days after transplantation in combination with reduced-dose tacrolimus and corticosteroids. Everolimus has also been used with tacrolimus with similar results as sirolimus.[123] Everolimus appears to have less of an effect on wound healing and thus may potentially be used earlier after transplantation.

Early cyclosporine withdrawal has been studied in patients receiving sirolimus-based immunosuppressive protocols. Ideal candidates are patients who have not had a recent or severe rejection episode and have adequate kidney function 3 months after transplant. Rejection occurred in 5.6% of patients after discontinuation of cyclosporine and no difference in graft survival was noted. Long-term follow-up (2 years) showed improved kidney function and blood pressure without an increase in acute rejection or graft loss in patients who discontinued cyclosporine.[112] Similar results have been demonstrated with everolimus.[123]

mTOR inhibitors have demonstrated efficacy to reduce CNI use and nephrotoxicity in liver, heart, and lung transplant patients.[122] mTOR inhibitors have also been investigated in liver transplant patients as a means to reduce the recurrence of hepatitis C and hepatocellular carcinoma.[122] They may also reduce the incidence of chronic rejection after heart transplantation.[65,73]

Adverse Effects

Both everolimus and sirolimus are associated with dose-related myelosuppression. Thrombocytopenia is usually seen within the first 2 weeks of sirolimus therapy but generally improves with continued treatment; leukopenia and anemia are also typically transient.[121,122] Sirolimus trough serum concentrations greater than 15 ng/mL (μg/L; 16 nmol/L) have been correlated with thrombocytopenia and leukopenia.[121] Hypercholesterolemia and hypertriglyceridemia are also common in patients receiving everolimus or sirolimus. The proposed mechanism of this adverse effect is overproduction of lipoproteins or inhibition of lipoprotein lipase. Peak cholesterol and triglyceride concentrations are often seen within 3 months of sirolimus initiation but usually decrease after 1 year of therapy and can be managed by reducing the dose, discontinuing sirolimus, or initiating therapy with an HMG-CoA reductase inhibitor or fibric acid derivative. Dyslipidemia associated with sirolimus may not be a major risk factor for early cardiovascular complications following kidney transplantation.[121] Delayed wound healing and dehiscence could be a result of inhibition of smooth muscle proliferation and intimal thickening.[121] For this reason, mTOR inhibitors are infrequently administered to transplant recipients in the immediate post-operative period. Mouth ulcers are observed in as many as 60% of patients treated with sirolimus and appear to be dose-related.[121] Reversible interstitial pneumonitis has been described in kidney, liver, and heart-lung transplantation recipients.[112] Despite their similarities, everolimus and sirolimus do have some differences likely related to differences in distribution. Sirolimus appears to enhance CSA neurotoxicity and both CSA and TAC nephrotoxicity, whereas everolimus did not.[122] Other adverse effects of sirolimus include increased liver enzymes, hypertension, rash, acne, diarrhea, and arthralgia (see Table 109-6).

Drug-Drug and Drug-Food Interactions

The major metabolic pathway for everolimus and sirolimus is CYP3A4; thus, the drug interactions mediated by induction or inhibition of the CYP3A4 enzyme system are similar to those seen with cyclosporine and tacrolimus (see Table 109-5). Administration of the microemulsion formulation of cyclosporine with sirolimus increases the AUC and trough sirolimus serum concentrations: this has not been observed with the standard formulation of cyclosporine. Conversely, cyclosporine concentrations and AUC are increased when it is given concomitantly with sirolimus. The mechanism is proposed to be competitive binding to CYP3A4 and P-glycoprotein.[121,122] Concomitant administration of tacrolimus does not affect sirolimus concentrations.[121] Although everolimus AUC was increased by the administration of a single dose of the microemulsion cyclosporine formulation, no specific recommendations for dose timing are given. It should be expected, however, that any changes in CSA dose may also necessitate a modification of everolimus dose and increased attention to therapeutic drug monitoring.[121]

As with cyclosporine and tacrolimus, grapefruit juice increases sirolimus concentrations. Administration of sirolimus with a high-fat meal is associated with a delayed rate of absorption, decreased C_{max}, and increased AUC, indicating an increased drug exposure, whereas the half-life remains unchanged.[121] Conversely, administration of everolimus with a high-fat meal was associated with decreases in both C_{max} and AUC.[122]

Dosing and Administration

The fixed sirolimus dosing regimen, approved for concomitant use with cyclosporine, includes a loading dose of 6 to 15 mg followed by 2 or 5 mg daily, respectively. However, loading doses are no longer recommended in clinical practice due to an increase in side effects. Therapeutic monitoring of sirolimus is routinely performed using whole-blood concentrations measured by HPLC, which is specific for the parent compound. For everolimus, a starting dose of 0.75 mg twice daily is indicated in regimens that contain cyclosporine, corticosteroids, and basiliximab induction. Target serum concentrations are 3 to 8 ng/mL (mcg/L; 3.1-8.4 nmol/L).

Co-Stimulatory Signal Inhibitor

Belatacept, derived from abatacept, is the only drug currently approved for use in solid-organ transplantation in this class of immunosuppressive agents. Belatacept may ultimately replace calcineurin inhibitors in the majority of immunosuppressive regimens given the lack of toxicities frequently seen with CNIs, especially nephrotoxicity.[23] Belatacept is only approved for kidney transplantation.

Pharmacology/Mechanism of Action

Belatacept is a selective co-stimulation blocker that binds co-stimulatory ligands (CD80 and CD86) on antigen-presenting cells, preventing interaction with CD28 on T cells (see Fig. 109-2). The interaction of CD80 and CD86 with CD28 is required for the initiation of "signal 2," the co-stimulatory signal that leads to the activation and proliferation of T-cells. Thus, blockade of CD80 and CD86 prevents T-cell activation.[124]

Pharmacokinetics

Belatacept, which is only available as an intravenous formulation, has a volume of distribution of 0.11 L/kg, a half-life of approximately 11 days and is not affected by impaired kidney or liver function.

Efficacy

Belatacept and cyclosporine exhibit similar efficacy in terms of both patient and graft survival in first time kidney transplant recipients. Cyclosporine users experienced more chronic allograft nephropathy at month 12, while the belatacept users experienced more frequent and more severe ACR. Despite this, the measured GFR was 13 to 15 mL/min (0.22-0.25 mL/s) higher in the belatacept group compared to the cyclosporine group, a trend that persisted for 7 years.[125] Additionally, belatacept-treated patients had better blood pressure control and lower lipid concentrations as well as less diabetes than CNI-treated patients. This finding may underlie the mortality difference observed at 7 years of follow-up.[23] Compared to tacrolimus, ACR is more common among kidney transplant recipients receiving belatacept, whereas the incidence of metabolic and neurologic toxicities is less common.[126] Conversion from CNI-based regimens to belatacept in kidney transplant recipients with stable kidney function leads to improved GFR from baseline.[127,128] However, acute rejection occurs more frequently in patients who switch to belatacept, compared with patients who remain on CNI.[23]

Use of belatacept in liver transplant patients has been associated with increased graft loss and death.[36,124] There is limited post-marketing experience with belatacept in heart and lung transplant recipients, though this is an area of ongoing interest.[127,129]

Adverse Effects

Belatacept is generally well tolerated. Adverse effects among belatacept recipients include anemia, neutropenia, diarrhea, urinary tract infections, headache, and peripheral edema.[23] Patients who are Epstein-Barr virus (EBV) naïve experienced a higher incidence of post-transplant lymphoproliferative disease (PTLD). PTLD typically occurs within the first 18 months of treatment and the majority occur in the central nervous system. There was no increase in incidence of PTLD in patients who are EBV-seropositive. As a result, belatacept carries a boxed warning for PTLD and is

contraindicated in patients who are EBV-seronegative. Belatacept has been associated with progressive multifocal leukoencephalopathy (PML).[23]

Drug-Drug and Drug-Food Interactions

There are no known drug or food interactions with belatacept.

Dosing and Administration

Potential belatacept recipients must be screened for EBV-serostatus prior to initiation of therapy. Only patients who are EBV-seropositive should receive belatacept due to the increased risk of PTLD in EBV-seronegative patients. As a primary immunosuppressant for first time kidney transplants, belatacept is administered as 10 mg/kg intravenously over 30 minutes on days 0, 5, 14, 28, and at the end of weeks 8 and 12. Thereafter, the dose is reduced to the maintenance dose of 5 mg/kg administered IV over 30 minutes every 4 weeks beginning at week 16.

When converting to belatacept from a CNI-based regimen, the proposed dosing schedule is 5 mg/kg IV administered every 2 weeks for 5 doses on days 0, 14, 28, 42, and 56, then every 4 weeks thereafter. The CNI dose should be decreased by 50% after the second dose of belatacept and then discontinued after the fourth dose.[23]

Investigational Agents

Rituximab

Rituximab is a chimeric monoclonal antibody against the CD20 receptor found on selected populations of B cells. While it is FDA-approved for non-Hodgkin lymphoma and rheumatoid arthritis, it has also been used for the treatment and prevention of antibody-mediated rejection and post-transplant lymphoproliferative disorders.[130] In highly sensitized patients, rituximab administration prior to transplant suppresses alloantibody levels.[131] However, when used in kidney transplant recipients with active AMR, administration of rituximab has failed to consistently demonstrate efficacy.[132] In PTLD, rituximab is most effective in patients with CD20-positive malignancies.[130]

Bortezomib

Bortezomib, a proteosomal inhibitor that is FDA-approved for the treatment of multiple myeloma, has been used in the treatment of AMR. Among patients with AMR who received four doses of bortezomib 1.3 mg/m^2 on days 1, 4, 7, and 11 with plasmapheresis, bortezomib was effective in lowering DSA by 50%.[72] Another series showed a benefit of bortezomib over rituximab.[72] However, bortezomib is associated with a high incidence of side effects (up to 33% required hospitalization) that may include diarrhea/dehydration, nausea, edema, thrombocytopenia, infections, and peripheral neuropathy.[72]

EVALUATION OF THERAPEUTIC OUTCOMES

The success of transplantation can be measured in terms of length of graft and patient survival as well as improvements in quality of life. Several donor and recipient factors that have an impact on graft and patient survival have been identified. The greatest risks to short-term graft survival are technical/surgical complications and acute rejection. Routine surveillance of appropriate biochemical markers and serum drug concentrations is essential to minimize the potential for acute rejection. These parameters should be assessed daily to weekly for the first 1 to 3 months after transplantation.

Monitoring for recipients of all solid-organ transplants should include complete blood counts, serum electrolyte concentrations, serum creatinine and blood urea nitrogen concentrations, and the appropriate serum drug concentrations. Liver function tests should also be evaluated using the same schedule in liver transplantation recipients. Routine biopsies are necessary to monitor for acute rejection in lung and heart transplantation recipients. As the time after transplantation increases, the frequency of monitoring decreases. Once 3 months have elapsed after transplantation, monitoring of these parameters can be reduced to biweekly or monthly for most patients. Table 109-8 depicts a typical post-transplantation laboratory monitoring plan. Long-term graft survival of all solid-organ transplants is limited by chronic rejection, a complication with few effective therapies which often necessitates re-transplantation.

TABLE 109-8

Laboratory Monitoring After Transplantation

	1-2 Weeks	1 Month	2-4 Months	4-12 Months	>12 Months
SCr/BUN	Daily	1-2 times per week	Every 1-2 weeks	Monthly	Every 1-2 months
Chemistries[a]	Daily	1-2 times per week	Every 1-2 weeks	Monthly	Every 1-2 months
Liver function tests[b]					
Kidney or heart recipient	Once	Once	Monthly	Every 1-3 months	Every 1-3 months
Liver recipient	Daily	1-3 times per week	Every 1-2 weeks	Monthly	Every 1-2 months
Immunosuppressant concentrations	Daily	1-2 times per week	Every 1-2 weeks	Monthly	Every 1-2 months
Complete blood count[c]	Daily	1-2 times per week	Every 1–2 weeks	Monthly	Every 1-2 months
Lipid panel[d]	Once	Every 3 months	Every 3 months	Every 3 months	Every 3 months
HbA_{1c}	Once	Every 3 months	Every 3 months	Every 3 months	Every 3 months

BUN, blood urea nitrogen; HbA_{1c}, hemoglobin A1c; SCr, serum creatinine.

[a]Chemistries include sodium, potassium, chloride, CO_2 content, magnesium, calcium, phosphorus, and blood glucose.

[b]Liver function tests include total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transpeptidase (GGTP), and alkaline phosphatase.

[c]Complete blood count includes white blood cells (WBC), red blood cells (RBC), platelets, and +/- differential.

[d]Lipid panel includes total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride.

IMMUNOSUPPRESSION-RELATED COMPLICATIONS

A fine counterbalance exists between under and over-immunosuppression. Beyond the first year post-transplant, death with a functioning graft is mostly attributed to cardiovascular disease, infection, and malignancy.[133] CNIs and corticosteroids, mainstays of maintenance immunosuppression, both contribute to cardiovascular disease-related risk factors including new-onset hypertension, diabetes, hyperlipidemia, and chronic kidney disease. All immunosuppressive agents inherently increase the risk of infection and impair cancer-related surveillance, which may lead to either de novo cancer post-transplant or cancer recurrence.[134] Routine surveillance including assessment and treatment of cardiovascular risk factors, along with vaccinations and age-appropriate cancer screening, are vital to ensure long-term patient survival. The following sections will review immunosuppression-related complications including cardiovascular disease, infections, and malignancy.

Cardiovascular Disease

Cardiovascular disease is a leading cause of morbidity and mortality in transplant patients.[135] Hypertension, hyperlipidemia, and diabetes are common

complications in transplanted recipients and are independent risk factors for cardiovascular disease.

Hypertension

Corticosteroids, tacrolimus, cyclosporine, and impaired kidney graft function may all contribute to post-transplantation hypertension. Calcineurin inhibitor-associated hypertension may be due to increased endothelin production as well as stimulation of the sympathetic and renin-angiotensin systems.[136] In addition to the propensity to cause peripheral vasoconstriction, CNIs promote sodium retention, resulting in extracellular fluid volume expansion. Tacrolimus appears to have less potential to induce hypertension following transplantation than cyclosporine.[99,136,137]

Dihydropyridine calcium channel blockers have traditionally been the first-line agents to treat hypertension after transplantation.[136] They may ameliorate the nephrotoxic effects of CNIs and improve renal hemodynamics.[138] ACEIs and angiotensin II receptor blockers have traditionally been avoided in kidney transplantation recipients, especially in the perioperative period, because of the potential for hyperkalemia and negative influence on glomerular filtration rate. When ACEIs or angiotensin II receptor blockers are used in patients after transplant, serum creatinine and potassium concentrations should be monitored closely. If the increase in serum creatinine is greater than 30% within 1 to 2 weeks after initiating ACEIs or angiotensin II receptor blockers, then other alternatives should be considered (see Chapter 65).

Multiple antihypertensive agents are usually necessary to achieve the goal of blood pressure in transplant recipients; consequently, the addition of a β-blocker, diuretic, or centrally acting antihypertensive may also be necessary. Calcineurin inhibitor-induced hypertension is often salt-sensitive, making it responsive to diuretics. Central-acting agents (eg, clonidine) are used often as adjunctive therapy in transplantation recipients who are unable to achieve blood pressure control with first-line pharmacotherapy agents. There are no universal goals for blood pressure in transplant recipients. Most guidelines indicate a goal between 130-140/80-90 depending on other compelling co-morbid disease states.[136]

Hyperlipidemia

Hyperlipidemia may be exacerbated by corticosteroids, calcineurin inhibitors, and mTOR inhibitors.[74,75] Corticosteroids promote insulin resistance and a decrease in lipoprotein lipase activity, as well as excessive triglyceride production. CNIs may decrease the activity of the low-density lipoprotein (LDL) receptor or lipoprotein lipase, altering LDL catabolism.[74] Tacrolimus appears to have less potential than cyclosporine to induce hyperlipidemia.[99] Controversy remains whether the management of hyperlipidemia in transplant recipients should be more aggressive than current guidelines for the general population (see Chapter 32).[75,139] Aggressive lipid lowering may not only arrest the progress or prevent the complications of atherosclerosis but may also promote graft survival in kidney and heart transplant recipients. Current recommendations suggest monitoring lipid panels 2 to 3 months after transplantation and annually thereafter.[61,75]

HMG-CoA reductase inhibitors should be used with caution in transplantation recipients because of the risk of rhabdomyolysis when these agents are combined with CNIs.[104] However, beyond their impact on hyperlipidemia, HMG-CoA reductase inhibitors also have immunomodulatory effects on MHC expression and T-cell activation, and they reduce cardiac allograft rejection and extend life in heart transplant recipients.[104]

Concurrent use of simvastatin and cyclosporine is contraindicated due to the increased risk of rhabdomyolysis.[139] The concurrent use of medications known to increase the risk of myopathy (such as gemfibrozil) should be avoided.[104] Baseline and follow-up creatinine phosphokinase measurements (every 6 months) have proven useful in identifying patients with subclinical rhabdomyolysis. HMG-CoA reductase inhibitors not metabolized by CYP3A4 may be preferred owing to their diminished risk of CNI-associated drug-drug interactions. Close monitoring of liver function is recommended in all transplant recipients.[75,139]

For transplant patients who have hypertriglyceridemia refractory to dietary intervention, fish oil and fibric acid derivatives are generally well-tolerated, effective alternatives (see Chapter 32). Fibric acid derivatives are most effective in lowering serum triglyceride concentrations. The novel PCSK9 inhibitors have been used in heart transplant recipients who are intolerant to HMG-CoA reductase inhibitors or those who require further LDL lowering therapy, but evidence to support this practice in other solid-organ transplant recipients is lacking.[140]

Post-Transplantation Diabetes Mellitus

Corticosteroids and CNIs can impair glucose control in patients with pre-existing diabetes and may cause post-transplantation diabetes mellitus (PTDM) in 5% to 30% of solid-organ transplant recipients.[70,75,98] Corticosteroids induce insulin resistance and impair peripheral glucose uptake, whereas CNIs appear to inhibit insulin production.[74] Tacrolimus seems to be more diabetogenic than cyclosporine.[99] Other possible risk factors that have been identified for PTDM include African American race or Hispanic ethnicity, age greater than 40 years at time of transplant, family history, and obesity, as well as CMV and hepatitis C virus infection.[74]

Up to 40% of patients with PTDM will require insulin therapy.[74] In patients with post-transplant diabetes who can be adequately managed with only oral hypoglycemics, agents such as dipeptidyl peptidase 4 (DPP-4) inhibitors, thiazolidinediones (TZDs), and sulfonylureas may be reasonable choices. Agents that do not undergo extensive renal elimination may be preferred to reduce the incidence of hypoglycemia and toxicity in the setting of drug accumulation due to end-organ dysfunction. Metformin should be used with caution because of the risk of lactic acidosis in those with impaired kidney function but is generally well-tolerated and may be associated with improved long-term outcomes.[141] Short-term use of SGLT2 inhibitors has been endorsed in transplant patients.[142]

Frequent blood glucose monitoring is imperative in the early postoperative phase to improve glucose control and to identify those with PTDM. Changes in kidney function secondary to CNI-associated nephrotoxicity, acute rejection, or other causes in kidney transplant recipients may affect elimination of many hypoglycemic agents, including insulin, and may result in hyper- or hypoglycemia. Dose changes of immunosuppressant drugs also affects glycemic control. Tapering of immunosuppressive medications may result in reduced insulin requirements, whereas corticosteroid pulses for the treatment of rejection may result in increased insulin requirements.

Infection

Increased risk of infection is a natural consequence of pharmacologic immunosuppression. Many infections in solid-organ transplant recipients, including cytomegalovirus and fungal infections, are reviewed in Chapter 145.

Polyomavirus-associated nephropathy (PVAN) is an important cause of impaired kidney function in kidney transplant recipients.[143] Primary infection with BK virus occurs in childhood as an asymptomatic infection in 50% to 90% of the general population. The precise mechanism of transmission is not clear but is suspected to be via the oral or respiratory routes. The virus may remain latent primarily in the genitourinary tract until reactivation as the result of compromised immune function. Reactivation can be detected by measuring the presence of BK virus in the urine or plasma, a finding that is seen in approximately 30% to 40% of kidney transplant recipients, although it does not progress to nephropathy in the majority of patients. However, BK viremia (if it develops) has been noted to progress to allograft nephropathy in 50% of patients.[143] The development of BK virus nephropathy results in graft loss in about 46% of affected patients.[143]

All kidney transplant recipients should be screened for urinary BK virus replication monthly for the first 3 to 6 months after transplant, and every 3 months thereafter for the first year.[75,143] Screening for BK virus in serum should also occur any time the serum creatinine is elevated without a known cause and after treatment of acute rejection. Treatment of BK virus should be initiated when plasma concentrations persist above 10,000 copies/mL (10×10^6/L).[75,143] The first line of treatment is to reduce immunosuppressive medications, targeting tacrolimus trough concentrations of <6 ng/mL (mcg/L; 7.4 nmo/L), cyclosporine <150 ng/mL (mcg/L; 125 nmol/L), sirolimus troughs <6 ng/mL (mcg/L; 6.6 nmol/L) or total daily mycophenolate mofetil doses of <1,000 mg.

Malignancy

Although advances in immunosuppression have decreased the incidence of acute rejection and increased patient survival, they have also increased the solid-organ transplant recipients' lifetime exposure to immunosuppression. While the precise mechanism is unclear, post-transplantation malignancy seems to be related to the overall level of immunosuppression, as evidenced by a difference in the rates of malignancy associated with quadruple versus triple versus dual immunosuppressant regimens. The risk of *de novo* malignancy in transplantation recipients is increased threefold to fivefold relative to the general population, and the risk of lung and colon cancers may be as much as doubled in kidney transplant recipients.[115,144] A number of cancers that are uncommon in the general population occur with much higher prevalence in transplantation recipients: post-transplantation lymphomas and lymphoproliferative disorders (PTLD), Kaposi sarcoma, renal carcinoma, in situ carcinomas of the uterine cervix, hepatobiliary tumors, and anogenital carcinoma are a few examples.[144]

Skin cancers are the most common malignancy. Factors that may predispose transplant recipients to skin cancers include sun exposure, the use of immunosuppressive medications, and concomitant use of medications that increase the risk of phototoxicity.[145] The mTOR inhibitors have a theoretical benefit in reducing the development of malignancy by way of antiproliferative effects. In fact, a decreased incidence of malignancy may be observed in patients receiving mTOR inhibitors versus CNIs, and conversion to mTOR inhibitors may result in regression of Kaposi sarcoma.[144]

PTLD encompasses a broad spectrum of disorders, ranging from benign polyclonal hyperplasia to malignant monoclonal lymphomas. Factors that predispose patients to PTLD include Epstein-Barr virus seronegativity at transplantation and intense immunosuppression, particularly with lymphocyte-depleting agents. Non-renal transplantation recipients are more likely to develop PTLD secondary to the intensive immunosuppression used to reverse rejection. Treatment of life-threatening PTLD generally includes severe reduction or cessation of immunosuppression. Other options include systemic chemotherapy or rituximab.[144]

Post-transplantation malignancies appear at an average of 5 years after transplantation and their incidence increases with the increasing length of follow-up. As many as 72% of solid-organ transplant recipients surviving greater than 20 years may be affected. Malignancy accounts for 11.8% of deaths after cardiac transplantation and is the single most common cause of death in the 6th to the 10th post-transplant years.[144]

CLINICAL BOTTOM LINE

Transplantation is a lifesaving therapy for several types of end-organ failure. Advances in the understanding of transplant immunology have produced an unprecedented number of choices in terms of immunosuppression. The increasing number of effective immunosuppressive therapies offers clinicians diverse ways to prevent allograft rejection.

However, the vast array of currently available immunosuppressive agents make it increasingly difficult to evaluate their long-term efficacy. Clinicians must be keenly aware of the adverse effects of immunosuppressive medications and their management in order to optimize the care of the transplanted patient.

ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitor
ACR	acute cellular rejection
AMR	antibody-mediated rejection
APC	antigen-presenting cell
ATG	antithymocyte globulin
ATN	acute tubular necrosis
AUC	area under the concentration curve
C_2	concentration 2 hours after dose
C_{peak}	peak concentration
CI	calcineurin inhibitors
CMV	cytomegalovirus

CYP	cytochrome P450 liver enzyme system
DAA	direct acting antivirals
DGF	delayed graft function
EBV	Epstein-Barr virus
ESKD	end-stage kidney disease
FKBP	FK506-binding protein
GI	gastrointestinal
HBIg	hepatitis B immunoglobulin
HLA	human leukocyte antigen
HMGCoA	hydroxy-3-methylglutaryl-coenzyme A
HPLC	high-performance liquid chromatography
IFN	interferon
IFTA	interstitial fibrosis and tubular atrophy
IL-2R	interleukin 2 receptor
IMPDH	inosine monophosphate dehydrogenase
LAS	lung allocation score
LDL	low-density lipoprotein
MELD	model for end-stage liver disease
MHC	major histocompatibility complex
6-MP	6-mercaptopurine
MPA	mycophenolic acid
MPAG	mycophenolic acid glucuronide
MRP2	multidrug-resistance-associated protein 2
mTOR	mammalian target of rapamycin
NFAT	nuclear factor of activated T lymphocytes
NODAT	new-onset diabetes after transplantation

OATP	organic anion-transporter proteins
OKT3	muromonab-CD3
PD-L1	programmed death ligand 1
PML	progressive multifocal leukoencephalopathy
PRA	panel of reactive antibodies
PSI	proliferation signal inhibitor
PTLD	post-transplantation lymphoproliferative disorder
PVAN	polyomavirus associated nephropathy
RIA	radioimmunoassay
REMS	risk evaluation and mitigation strategy
TPMT	thiopurine S-methyltransferase

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SELF-ASSESSMENT QUESTIONS

1. Which of the following is NOT true regarding induction immunosuppression strategies?

   A. They are used patients at high risk of rejection.

   B. They are used to delay the initiation of nephrotoxic medications.

   C. They refer to use of antibody agents.

   D. They include calcineurin inhibitors.

2. Which class of medications should be given to all heart transplant recipients in order to prevent/mitigate the development of chronic rejection (ie, coronary allograft vasculopathy)?

   A. HMG-CoA reductase inhibitors (ie, statins)

   B. Bile acid sequestrants

   C. Fibrates (eg, gemfibrozil)

   D. PCSK9 inhibitors

3. A 48-year-old male received a heart transplant 6 months ago. He has preexisting kidney impairment, hypertension (BP = 160/95) and hyperlipidemia. His most recent heart biopsy showed no signs of rejection. His current immunosuppressant regimen is: tacrolimus 3 mg by mouth twice a day (last concentration 11 ng/mL [mcg/L; 13.6 nmol/L]), mycophenolate mofetil 1,000 mg by mouth twice daily and prednisone 5 mg by mouth daily. Which of the following is true?

   A. Replacing tacrolimus with everolimus may improve his hypertension and hyperlipidemia

   B. Replacing tacrolimus with sirolimus may improve his kidney function and hypertension

   C. Replacing tacrolimus with cyclosporine may improve his hypertension and kidney function

   D. Replacing tacrolimus with sirolimus may improve his kidney function and hemoglobin

4. A 34-year-old female kidney transplant recipient is receiving an immunosuppressant regimen consisting of tacrolimus and mycophenolate mofetil. She is 3 months post-transplant and has stable kidney function. She is complaining of excessive hair loss. What change might the clinician consider?

   A. Change mycophenolate to azathioprine

   B. Change tacrolimus to either cyclosporine or belatacept

   C. Add everolimus to her regimen

   D. Add belatacept to her regimen

5. Which of the following immunosuppressants has the longest half-life?

   A. Cyclosporine

   B. Tacrolimus

   C. Prednisone

   D. Sirolimus

6. A 47-year-old, 70-kg lung transplant recipient is currently receiving the following medications: tacrolimus, mycophenolate mofetil, sirolimus, prednisone, valganciclovir, sulfamethoxazole-trimethoprim thrice weekly and nystatin. His most recent laboratory evaluation revealed: WBC 2,100/mm^3 (2.1 × 10^9/L) Hgb 11.8 g/dL (118 g/L; 7.32 mmol/L), SCr 1.3 mg/dL (115 µmol/L), and tacrolimus 11 ng/mL (mcg/L; 13.6 nmol/L). Which of the following is NOT likely contributing to his leukopenia?

   A. Mycophenolate mofetil

   B. Sirolimus

   C. Tacrolimus

   D. Valganciclovir

7. Which of the following immunosuppressive medication is most likely to have increased AUC during treatment of esophageal candidiasis infection with fluconazole?

   A. Cyclosporine

   B. Prednisone

   C. Mycophenolic Acid

   D. Belatacept

8. A 57-year-old male with a kidney transplant is diagnosed with post-transplant BK nephropathy. His current immunosuppressant regimen consists of: tacrolimus 6 mg by mouth twice daily and sirolimus 3 mg by mouth daily. Which of the following changes should the clinician consider?

   A. Increase sirolimus dose/trough goal

   B. Change sirolimus to mycophenolate

   C. Decrease tacrolimus dose/trough goal

   D. Change tacrolimus to belatacept

9. Which of the following statements is true?

   A. Tacrolimus increases MPA concentrations due to interference with enterohepatic recycling of MPAG.

   B. Febuxostat inhibits xanthine oxidase, the enzyme responsible for elimination of MPAG.

   C. Phenytoin decreases tacrolimus concentrations by inducing activity of CYP 3A4 enzymes.

   D. Magnesium-containing antacids cannot be used concurrently with azathioprine.

10. A 42-year-old female is being discharged after receiving a heart transplant 2 weeks ago. Which of the following is NOT an appropriate monitoring plan for the next month?

    A. Serum creatinine should be monitored once or twice a week.

    B. Liver function tests should be monitored once or twice a week.

    C. Tacrolimus concentrations should be monitored once or twice a week

    D. Complete blood counts should be monitored monthly.

11. A 32-year-old male received a kidney transplant 3 weeks ago secondary to type I diabetes. He presents to clinic with a blood pressure of 160/98 and

HR 62. He is afebrile. Recent laboratory values include Scr 1.1mg/dL (97 µmol/L) (nadir 1.0 mg/dL [88 µmol/L]), potassium 4.1 meq/L (mmol/L), WBC 4,100/mm^3 (4.1 × 10^9/L). His current medications include tacrolimus 8 mg twice daily (trough 9.8 ng/mL [mcg/L; 12.2 nmol/L]) and mycophenolate sodium 720 mg twice daily. Choose the most appropriate antihypertensive agent to initiate.

A. Amlodipine

B. Diltiazem

C. Lisinopril

D. Metoprolol

12. Which of the following statements regarding belatacept is true?

A. There are both immediate and extended release formulations.

B. Patients who are EBV seropositive are ineligible for treatment with belatacept

C. Belatacept is used in immunosuppressive regimens in combinations with other immunosuppressants, such as CNI, antimetabolites, mTOR inhibitors, and/or corticosteroids

D. Belatacept is used as single-agent immunosuppression

13. A 58-year-old liver transplant recipient presents to the transplant clinic with a blood glucose log that she has been keeping at home, which indicates a new diagnosis of post-transplant diabetes. Which of the following statements is true regarding initiation an anti-hyperglycemic agent in a solid-organ transplant recipient?

A. Metformin should be avoided due to risk for lactic acidosis.

B. Dipeptidyl-peptidase 4 inhibitors are often used as first-line therapy for patients who are candidates for oral anti-hyperglycemic treatment.

C. Insulin should be the first anti-hyperglycemic agent selected for all solid-organ transplant recipients owing to its unlimited efficacy and titratable dosing.

D. Very few antihyperglycemic agents are renally excreted and thus it is generally not necessary to evaluate for end-organ function prior to selecting an agent.

14. A 46-year-old lung transplant recipient presents to the transplant clinic complaining of new onset shortness of breath. Her current immunosuppressive medications include tacrolimus (goal 8-10 ng/mL [mcg/L; 9.9-12.4 nmol/L]), mycophenolate 250 mg twice daily, and prednisone 5 mg daily. Bronchoscopy and transbronchial biopsy are performed confirming mild cellular rejection. Which of the following is the most appropriate pharmacotherapy plan?

A. Methylprednisolone pulse followed by taper

B. Methylprednisolone pulse followed by taper with a simultaneous increase in mycophenolate dose, targeting 1000 mg twice daily

C. Antithymocyte globulin 7.5 mg/kg over 5 to 7 days

D. Rituximab 375 mg/m^2 ×1 dose

15. Which of the following statements are false regarding the use of mTOR inhibitors in solid-organ transplant recipients?

A. They are only approved for use in liver transplant recipients who have new-onset kidney disease post-transplant.

B. They are susceptible to drug interactions if used concurrently with CYP 3A4 inhibitors/inducers.

C. They require therapeutic drug monitoring.

D. They are difficult to tolerate owing to a multitude of potential ADEs.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Calcineurin inhibitors are not used for induction immunosuppression. These agents are given as part of maintenance immunosuppression (long-term).

2. **A.** The statin medications have been shown to prevent coronary allograft vasculopathy in several well-designed clinical trials. As such, these agents should be given to all heart transplant recipients. The other choices have not proven effective in preventing CAV.

3. **B.** Replacing tacrolimus with sirolimus would reduce the risk of renal injury and hypertension that are both common side effects of tacrolimus. The other choices are not correct because the changes to the medication regimen suggested are not correctly matched with side effects of the respective drugs involved in the swap.

4. **B.** Alopecia is a known side effect of tacrolimus; however it is not associated with the use of either cyclosporine or belatacept. The possible benefits should be cautiously weighed against the risks of converting to either a belatacept- or cyclosporine-based immunosuppression regimen. Refer to Table 6 for further study of drug-related ADE.

5. **D.** Sirolimus has the longest half-life of the available options (60-110 hours).

6. **C.** Leukopenia is a common side effect of mycophenolate, sirolimus, as well as valganciclovir. Tacrolimus is rarely implicated in hematologic disturbances. Refer to Table 6 for further study of drug-related ADE.

7. **A.** Cyclosporine is a substrate of CYP 3A4, and therefore, the exposure will increase with concomitant use of fluconazole (CYP 3A4 inhibitor). Prednisone, mycophenolic acid, or belatacept are not metabolized via CYP 3A4.

8. **C.** As with most post-transplant opportunistic infections, a mainstay of management involves some reduction in net immunosuppression. Neither the substitution of mycophenolate for sirolimus or belatacept for tacrolimus would be beneficial in the setting of BK nephropathy.

9. **C.** Phenytoin is an inducer of CYP 3A4 and therefore decreases the serum concentrations of tacrolimus. See Table 5 for further study.

10. **D.** Once a patient is discharged two weeks after transplant, weekly monitoring is required for some time. As such, choice D is not correct, as waiting one month to follow up on the patient is not safe.

11. **A.** Dihydropyridine calcium channel blockers (DHP CCB) are routinely used as first line antihypertensive agents in solid-organ transplant recipients. Nodal blocking agents (eg, metoprolol or non-DHP CCB) would not be advised in this patient with baseline HR of 62 bpm, and initiating lisinopril may lead to an acute rise in serum creatinine that may require evaluation for acute rejection, technical/surgical complications, or other causes of posttransplant acute kidney injury.

12. **C.** Belatacept is available exclusively for intravenous administration, is not to be used in EBV seronegative patients due to the risk for post-transplant lymphoproliferative disease, and is not recommended for use as monotherapy.

13. **B.** Choice A is incorrect because while lactic acidosis is a concern in post-transplant recipients, the risk is minimal and metformin is often used. Choice D is also incorrect as many anti-hyperglycemic agents are renally excreted. Although patients may be started on insulin, it is not universally considered first line, therefore Choice B is correct.

14. **B.** For mild cellular rejection, treatment with high-dose IV cortico-steroids and simultaneous increase in background maintenance immunosuppression is warranted. If sub-optimal response is achieved, more intensive therapies may be considered thereafter. Refer to Fig. 109-3 for general approach to management of post-transplant rejection.

15. **A.** Choice A is false because mTOR inhibitors have several indications related to solid-organ transplantation.