Care Of The Organ Transplant Recipient

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Background: **Organ and tissue allografting is now a commonly performed procedure. Patients receiving allografts and immunosuppressive medication are no longer restricted to a few specialized centers and areas of the country. Because transplant recipients are leading longer and healthier lives, these patients are appearing in diverse medical settings where expertise in transplantation is not generally established. Because many generalist and specialist physicians can expect to treat this group of patients, it is important that information about the care of transplant patients and their particular problems and needs be made more accessible to other physicians.**

Methods: **The authors have compiled the most numerous questions and problems from referring physicians, emergency department physicians, and housestaff and have reviewed the recent literature pertinent to particular issues.**

Results and Conclusions: **This review addresses some of the common problems and myths that surround transplant recipients and discusses how best to initiate care for these patients, particularly when they seek treatment from a nontransplant physician. This review is not exhaustive, but rather a field guide to the initial care of this group of patients. The notion that only those with specialized knowledge can care for these individuals must now be relinquished so that these patients can enter the mainstream of medical care. (J Am Board Fam Pract 1993; 6:563-76.)**

The number of transplant centers and patients has grown markedly during the last decade. Many technical and immunologic advances have contributed to this remarkable growth. Both patient and graft survival have steadily increased during this period, even though organ transplant recipients have become older and have more comorbid conditions. Transplant operations are now considered commonplace in many medical centers. Although many recipients are cared for almost exclusively by their transplant center, the growth in transplantation, the extension of patient and graft survival, and the mobility of the United States public have contributed to the spread of transplant recipients to many types of medical settings where transplantation experience is not established.

There are a number of issues and concerns that affect transplant patients and nontransplant physicians attempting to care for them. We have organized this guide to help these physicians sort through many of the common problems and myths to provide both emergent and long-term care to these patients. This article is in no way intended to be a complete review of all the problems that might concern transplant recipients; for that we suggest the use of current textbooks of transplantation[1-3] or the specific area of need. Ultimately we encourage all nontransplant physicians to communicate early and regularly with the patient's transplant center to optimize the patient's care.

Submitted, revised, 7 July 1993.

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Methods

We have compiled a list of the most common questions, problems, and complications that confront the transplant patient's primary care physicians, emergency department physicians, consultants in a community setting, and medical and surgical housestaff not primarily involved in transplantation. Literature searches of particular topics were conducted to provide appropriate updating and references.

Common Myths

A mystique has developed around the transplantation process, aided and abetted by transplant physicians themselves. The inability to predict

outcomes, the occurrence of unusual infections and complications, and the seemingly capricious nature of immunosuppressive protocols have contributed to numerous misconceptions regarding the nature of transplant recipients, suggesting that only physicians with special knowledge are able to care for them (Table 1).

Stress Steroids

Ever since Fraser, et al.[4] and Lewis, et al.[5] published their case reports in the 1950s, it has been widely believed that any patient taking exogenous glucocorticoids has suppression of the hypothalamic-pituitary-adrenal axis and requires massive doses of supplemental exogenous "stress" steroids to meet the demands of physiologic stressors, such as general anaesthesia and major surgery. Studies in humans and primates show that the incidence of adrenal suppression as a result of exogenous steroids is much lower than previously suggested and that supraphysiologic doses of glucocorticoids are not necessary to meet the demands of stress.[6-9] In fact, only physiologic, base-line replacement doses of glucocorticoids (e.g., 7.5 mg prednisone or 30 mg hydrocortisone per day) are required to meet the demands of major operative stress. Our own studies in transplant recipients,[10] all of whom take glucocorticoids, confirm this dosage, and our current approach is to administer only base-line immunosuppressive drugs during periods of stress (e.g., surgery, sepsis, bleeding, hypotension). As most recipients receive 5 to 15 mg of prednisone per day, this amount approximates physiologic requirements. In our experience renal, pancreatic, and hepatic transplant recipients have had no episodes of adrenal insufficiency using this approach, and it avoids complications of high-dose corticosteroid administration, such as hyperglycemia, decreased white cell function, and wound healing.

There is sometimes confusion about the potency of available steroid preparations. By assigning hydrocortisone (or Solu-Cortef, cortisone or cortisol) a potency value of 1, prednisone has a value of 4, whereas prednisolone or methylprednisolone (Solu-Medrol) has a value of 5. Thus 4 mg of prednisolone equals 5 mg of prednisone, which equals 20 mg of hydrocortisone (Table 2). In clinical practice the difference between the potencies of prednisone and prednisolone is generally ignored. It should be noted that the inactive drug prednisone is metabolized to the active form, prednisolone, by the liver. Only prednisolone, therefore, should be administered to liver recipients and others with hepatic insufficiency or dysfunction.

Table 1. Common Myths about Transplant Recipients.

Common Myths	Clinical Knowledge
Patients need stress steroids to meet the demands of stress	Transplant patients do not need supraphysiologic stress steroids; give only daily immunosuppressive dose of glucocorticoid
Other disease processes are all the same (or different)	Inflammatory responses are blunted In evaluating symptoms, increase suspicion for complicated major illness and make liberal use of simple blood tests, radiographs, and cultures
Organs will be rejected immediately (or never rejected)	Rejection is uncommon in the setting of other acute illnesses Even long-functioning grafts will eventually be rejected if immunosuppression is stopped The best policy is to maintain the usual daily doses of immunosuppression

Other Disease Processes Are All the Same (or Different)

Two extreme views of abnormal function are frequently encountered. On one hand there is the belief that transplant recipients will exhibit common problems in a bizarre and unusual fashion or, alternatively, that their disease expression will be similar or identical to that of normal patients. It is important to consider that all transplant recipients receive immunosuppressant drugs (i.e., glucocorticoids, azathioprine, cyclosporine). These agents are anti-inflammatory and blunt the immune response to infection, ischemia, trauma, neoplasia, and other tissue insults. This blunting results in a decreased inflammatory cellular infiltrate in regions of tissue damage and a decrease in the production of proinflammatory cytokines.[11-16] Similar abnormalities are also found with more familiar disorders, such as advanced age, malnutrition, acquired immunodeficiency syndrome (AIDS), and metastatic neoplasia.[13,14] The result of these abnormalities is a spectrum of signs and symptoms of disease that are diminished in intensity when compared with those in the normal population. For example, diverticulitis with per-

Table 2. Relative Potencies of Glucocorticoid Preparations.

Generic Name	Trade Name	Relative Potency
Hydrocortisone sodium succinate	Solu-Cortef	1
Cortisone		1
Cortisol		1
Prednisone	Deltasone	4
Prednisolone	Sodium succinate	5
Methylprednisolone sodium succinate	Solu-Medrol	5

foration might present with dull, vague abdominal discomfort rather than with prominent peritonitis and rebound tenderness. Pneumonia might present with low-grade fever and a slight dry cough rather than with rigors and sputum production. Consequently, the rationale in evaluating and treating disease in transplant recipients is one of heightened suspicion. Seemingly minor complaints should elicit more complete examination and testing than would be allotted to a standard patient. Failure to adopt this approach can result in missing major life-threatening conditions.

The approach to an individual patient also depends on such factors as current dose of steroids, current allograft function, and interval between transplantation and the current problem. For example, a patient 3 months following hepatic transplantation taking 20 mg of prednisolone a day with poor graft function is obviously more immunosuppressed than a patient 5 years after renal allografting with a creatinine level of 1.1 mg/dL receiving 7.5 mg of prednisone a day. The former patient might have more subtle signs and symptoms of other problems than the latter.

Organs Will Be Rejected Immediately (or Never Rejected)

Some believe that a stable allograft will never be rejected, while others think that any minor abnormality can lead to catastrophic rejection. Because of these beliefs, transplant recipients at differing institutions sometimes receive immunosuppressants either far below or far above their normal doses. The body's ability to reject an organ and the tempo and severity of rejection vary according to the time interval since transplantation, current immunosuppressive drug doses, and current graft function.[17] In the examples cited above, a patient recently receiving a transplant, taking high-dose immunosuppression therapy, and displaying suboptimal graft function is more likely to undergo rejection than a patient with excellent function and minimal immunosuppression several years after transplantation. Unfortunately, rejection in an individual patient cannot be predicted; only a relative risk can be assigned.

In the setting of emergency treatment for an acute problem unrelated to allograft function, recipients generally do not undergo rejection, probably as a result of a generalized immune suppression that accompanies many major stresses.[13] In most acutely ill patients immunosuppression can therefore be maintained at their current levels without fear of rejection. Maintaining some immunosuppressive drugs is always required, however, because even long-functioning grafts will eventually be rejected if immunosuppression is stopped. As discussed above, stress-dose steroids are not required to meet the demands of an acute illness. Reducing dosages of immunosuppressive drugs because of systemic sepsis should be done only in consultation with the transplant center.

If immunosuppressive drugs must be administered intravenously, the following rules of thumb apply (Table 3): give the same dose of intravenous methylprednisolone as the patient was taking oral prednisone or prednisolone; use the same intravenous dose of azathioprine as the patient was taking orally; give one-third the oral cyclosporine dose as an intravenous infusion for 4 to 12 hours. In some cases in which transplant recipients are being treated for severe infection, a reduction of immunosuppressive medication is warranted to improve the chance for survival. In this circum-

Table 3. Conversion of Immunosuppressants from Oral to Parenteral Doses.

Drug	Oral	Conversion	Parenteral (iv)
Glucocorticoids	Prednisone Prednisolone	Same dose (mg)	Methylprednisolone
Azathioprine	Azathioprine tablet	Same dose (mg)	Azathioprine injection
Cyclosporine	Cyclosporine	Intravenous dose = 1/3 oral dose; infuse for 4 to 24 hours	Cyclosporine ampule for infusion

stance azathioprine and cyclosporine dosages are reduced or stopped, and prednisone is decreased to 7.5 mg daily (physiologic replacement dose). Consultation with or transfer to a transplant center should occur before such adjustments in immunosuppression are performed.

Common Problems

Infection

Infection (Table 4), while very common in transplant recipients, is no longer the most common cause of death; cardiovascular disease has taken first rank.[18] Liver, pancreas, and heart recipients receive cumulatively more immunosuppressive drugs than kidney recipients. Hepatic and cardiac function are essential to life, whereas pancreatic allografts have a higher rate of rejection. Consequently, infectious complications are common in recipients of these three organs.[19-21] The incidence and severity of infection vary depending on current or recent immunosuppression, current organ function, number of treated rejection episodes, use of such reagents as monoclonal or polyclonal anti-T cell sera (or both), and anatomic predisposition (e.g., biliary obstruction, neurogenic bladder).[18]

It is a common misconception that transplant recipients are subject to infection by any organism in their immediate environment. Our recipients have included school teachers, nurses, and physicians who sicken with common ailments no more often than their normal associates. When infections occur in organ recipients, however, the symptoms might be muted compared with those in other patients. The lesson is to be vigilant and not dismiss mild signs and symptoms that could be safely watched in patients not receiving immunosuppressive drugs.

Immunosuppression is associated with a higher incidence of unusual infections, and clinical suspicion must be increased accordingly. *Legionella*, tuberculosis, atypical mycobacteria, *Pneumocystis*, *Nocardia*, *Aspergillus*, *Listeria*, and other unusual organisms can cause infections in patients who have stable organ function and are on minimal immunosuppression years after transplantation. A careful history and physical examination, plus liberal culturing of appropriate samples, are major principles in the management of suspected infections in transplant patients.

Of particular concern in transplant patients is infection with viruses of the herpesvirus family: herpes simplex virus (HSV), varicella-zoster virus, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) (Table 5). HSV type I and HSV type II are frequently reactivated after transplantation and can become disseminated.[22] These infections will produce oral or genital lesions; however, they might not be characteristic, because steroids alter the dermal and epidermal response to virus. Tzanck preparations, cultures, and serologic tests are helpful in making a proper diagnosis. Acyclovir is useful for both prophylaxis and treatment of HSV infections; many programs normally give a short (30 to 60 days) course of low-dose acyclovir (200 mg orally twice or four times a day) to transplant recipients for prophylactic reasons, particularly when anti-T-cell antibodies have been administered. Withdrawal or reduction of azathioprine might be required to treat active infection.

Varicella-zoster virus can reactivate either as classical shingles in a dermatomal distribution or less commonly as disseminated disease with fever, malaise, pneumonia, or hepatitis. High-dose oral acyclovir (800 mg orally two to four times per day depending on the level of renal function) can be used for treatment of dermatomal zoster infections. Dissemination, however, should cause immediate hospital admission for intravenous acyclovir

Table 4. Infectious Complications That Occur in Transplant Patients.

Infection is the:	
Most common complication among hepatic, cardiac, and pancreatic recipients	
Second most common complication among renal recipients (after cardiovascular morbidity)	
Incidence and severity of infection depend upon:	
Current immunosuppression	
Current organ function	
Number of treated rejected episodes (i.e., cumulative immunosuppression)	
Recent use of antibody reagents for immunosuppression (i.e., OKT3,* MALG,† ATGAM‡)	
Anatomic predispositions	
Unusual organisms are:	
Mycobacterium tuberculosis	*Pneumocystis*
Mycobacterium avium intracellulare	*Aspergillus*
Nocardia	*Candida*
Listeria	
Legionella	

*OKT3 — a "pan-T" cell antigen.
†MALG — antilymphoblast globulin.
‡ATGAM — antithymocyte globulin.

Table 5. Herpesvirus Infections: Diagnosis, Prophylaxis, and Treatment.

Virus	Syndrome	Diagnosis	Prophylaxis	Treatment
Herpes simplex virus I & II	Localized or disseminated lesions	Serology, Tzanck test, culture	Acyclovir, 200 mg 2 to 4 times a day orally	Acyclovir, 800 mg 2 to 4 times a day, decrease immunosuppression
Varicella-zoster virus	Shingles Pneumonia Hepatitis	Serology, Tzanck test, histology	Acyclovir, 200 mg 2 to 4 times a day orally	Acyclovir, 800 mg 2 to 4 times a day, decrease immunosuppression
Epstein-Barr virus	Mononucleosis LPD* FUO†	Serology, immunofluorescence, or ELISA‡	Acyclovir, 200 mg 2 to 4 times a day orally	Acyclovir, 800 mg 2 to 4 times a day, decrease immunosuppression
Cytomegalovirus	FUO Pneumonia Hepatitis Colitis Encephalitis	Serology, histology, immunofluorescence	Acyclovir, 200 mg 2 to 4 times a day orally; ganciclovir, 2.5 mg/kg intravenously twice a day; CMV IgG, 150 mg/kg intravenously 5 doses over 6 weeks	Ganciclovir, 2.5 mg/kg intravenously twice a day, CMV IgG, decrease immunosuppression

*Lymphoproliferative disorder.
†Fever of unknown origin.
‡Enzyme-linked immunosorbent assay.

therapy; partial withdrawal of immunosuppression, especially azathioprine, might be required.[23]

EBV causes not only the usual mononucleosis syndrome but also is associated with post-transplant lymphoproliferative disease (LPD), a condition with malignant potential.[24-26] The EBV genome becomes incorporated into B lymphocytes, inducing a polyclonal proliferation of these cells. In the presence of immunosuppression, some of these clones escape immune surveillance and become autonomous. As the oligoclonal proliferation progresses, a single clone escapes normal immune regulation and a monoclonal B cell lymphoma results. LPD is associated with heavy immunosuppression, especially the use of antibody reagents, and concurrent EBV infection. Avoidance of excessive immunosuppression and prophylactic acyclovir administration are effective in decreasing the occurrence of LPD. Reduction or withdrawal of immunosuppressive drugs and acyclovir administration are sometimes effective therapeutic maneuvers, though they might be futile if the process has already become monoclonal and aggressive. LPD can masquerade as rejection or fever of unknown origin, and diagnosis can be difficult.

Cytomegalovirus infections are common after transplantation and include both reactivation or reinfection and primary CMV disease.[27-30] Classically, patients seek treatment 4 to 12 weeks after transplantation with fevers, constitutional symptoms, mild elevation of transaminase levels, thrombocytopenia, and leukopenia. The usual treatment for reactivation or reinfection disease is supportive care of symptoms, as the course is often self-limited. It might be necessary to stop azathioprine therapy because of leukopenia; steroid dosage should be reduced without sacrificing the safety of the graft. Reactivation disease after recent heavy immunosuppression or a primary infection even with standard immunosuppression, however, can progress to lethal systemic disease. Patients at high risk for primary infection are CMV-seronegative recipients (about 20 percent of the population) who have received organs or blood products from CMV-seropositive donors (about 80 percent of the population). Prophylactic therapy with high-dose oral acyclovir or intravenous ganciclovir plus CMV hyperimmune globulin substantially reduces the occurrence of CMV disease in this high-risk group. Progressive CMV disease is treated with ganciclovir, CMV hyperimmune globulin, and reduction or withdrawal of immunosuppressive drugs.

Urinary tract infections (Table 6) are extremely common; the incidence has approached 50 percent in some series of renal transplant recipients.[31] Unlike the normal population, immunosuppressed individuals are often relatively asymptomatic. The patient commonly presents with sepsis without preceding dysuria or pain. The organisms are the same as in community-acquired urinary tract infections.

Table 6. Site-Specific Infections and Their Characteristics.

Infection	Characteristics
Urinary tract infection	Up to 50% of incidence in renal transplants, often asymptomatic, same organisms as in community-acquired urinary tract infections
Pneumonia	Often subtle clinic presentation without cough, sputum, or rigors; chest x-ray film may look normal, arterial blood gas mandatory if pneumonia is suspected. "Normal" chest x-ray film, PaO_2, < 70 mmHg, probably requires bronchoscopy for definitive diagnosis, especially *Pneumocystis carinii* pneumonia or cytomegalovirus
Abdominal sepsis	Diverticulitis, cholecystitis, appendicitis — often subtle and atypical clinical presentations

The immunosuppressed patient can exhibit symptoms of pneumonia in unusual ways (Table 6). The cough and rigors of community-acquired infections might not be prominent, yet they can be rapidly progressive. Any transplant patient with a cough, mild fever, or shortness of breath must have a chest x-ray examination and arterial blood gas determinations. If the PaO_2 is < 70 mmHg on room air, admission is mandatory, and aggressive work-up and treatment must follow. This action frequently includes emergent bronchoscopy to obtain samples to confirm or deny the diagnosis of *Pneumocystis carinii* pneumonia (PCP) or CMV. It is often necessary to treat empirically without a microbiologic diagnosis. In such cases remember that erythromycin inhibits cyclosporine metabolism and can dramatically raise serum levels (see below); if possible, another drug should be substituted.

PCP and CMV pneumonias are particularly common in the transplant population. Patients often have signs and symptoms of fever and hypoxia, and a mild interstitial infiltrate appears on chest x-ray films. Although pneumonia caused by CMV usually occurs within the first 12 weeks following transplantation, occasionally it will occur later. PCP follows a similar pattern, so both must be considered in any patient. In organ transplant recipients, PCP pneumonia can be an explosive condition, unlike its presentation in the AIDS patient, where it tends to be more indolent; however, either presentation can occur. The diagnosis of both PCP and CMV pneumonias can be difficult because the chest radiograph often leads the physician to underestimate the extent of the disease; in fact, the chest film could be considered normal. A determination of PaO_2 is mandatory in the febrile transplant recipient in whom the source of fever is obscure. The PaO_2 level in both PCP and CMV pneumonias will usually be lower than the chest x-ray findings would suggest. Bronchoscopy with biopsies and bronchial brushings and washings are almost always necessary to establish the diagnosis of PCP or CMV pneumonia. If suspicion of either pneumonia is high, it is reasonable to start empiric therapy with ganciclovir or trimethoprim-sulfamethoxazole while bronchoscopy is being arranged.

Unexplained abdominal pain in the transplant recipient should always raise the specter of diverticular disease. Diverticulosis is extremely common in the dialysis population, particularly in those with autosomal dominant polycystic kidney disease, for whom the prevalence can approach 100 percent.[32] Early studies showed mortality levels of about 70 percent when diverticulae ruptured in immunosuppressed patients.[33] More recently, the mortality rate has fallen dramatically, probably because of earlier disease recognition and surgery.[34] In a similar fashion, cholecystitis can have very subdued features; empyema or even gangrene of the gall bladder can have minimal signs and symptoms. Gall bladder disease must also be considered in a patient with unexplained abdominal discomfort.

As with any patient, obtain proper cultures and radiologic studies. If no diagnosis is obvious, broad-spectrum antibiotic coverage including antiviral and antifungal agents might be necessary. Broad-spectrum coverage should have a definite limit, however, and be curtailed if no pathogen or disease process can be identified, usually within 48 to 72 hours, because immunosuppressed individuals have a greater chance of overgrowth of fungi than their more normal counterparts; immunosuppression, organ failure, antibiotic administration, and malnutrition all favor fungal infections.

Rejection

Rejection is often first announced by changes in some simple or routine laboratory tests (Table 7). In the stable recipient with good graft function who has had a transplanted organ for more than 1 year, it is recommended these simple tests be performed every 6 to 12 weeks. Rejection is confirmed by a variety of other more invasive procedures, particularly biopsy of the relevant organ.

Table 7. Initial and Confirmatory Tests of Rejection.

Organ	Initial Tests	Confirmatory Tests
Kidney	BUN, creatinine, complete blood count, urinalysis	Renal ultrasonography, nuclear medicine scan, biopsy, angiography
Liver	Liver function tests	Biopsy, ultrasonography of vessels and ducts, angiography, ERCP, PTC, serology
Pancreas	Glucose, urinary amylase	If simultaneous kidney-pancreas, evaluate for kidney rejection
Heart	Biopsy, electrocardiogram, chest x-ray film	Echocardiogram, Swan-Ganz
Lung	Arterial blood gasses, plasma thromboplastin factor	Biopsy, bronchography, angiography

If rejection is suspected, it is mandatory that the transplant center be contacted immediately and recommendations sought. Unless the patient is too unstable, transfer to the transplant center to perform definitive diagnosis and treatment will probably be recommended.

The classic description of acute renal allograft rejection lists fever, pain, and swelling over the graft, weight gain, and hypertension associated with a rise in the creatinine level as markers of rejection; however, this description was written before the availability of cyclosporine. With its use, all the so-called classic signs and symptoms of renal allograft rejection have disappeared, leaving only the creatinine level rise as a sign of rejection. Rejection of other organs is also most often asymptomatic. If laboratory abnormalities are picked up, confirmatory tests are required to rule out anatomic (technical), pharmacologic, or infectious problems; a biopsy of the allograft is often needed to confirm the diagnosis of rejection prior to instituting therapy (Table 7). The challenge for the nontransplant physician is to realize that clinical signs and symptoms are usually a very late sign of rejection and that liberal use of laboratory tests during frequent, routine, follow-up visits is important to diagnose rejection early.

Peptic Ulcer Disease

In the recent past, higher and more prolonged doses of steroids were used to prevent and treat rejection. As a result, peptic ulceration was believed to be common in transplant recipients, though this relation has been debated.[35] Medication regimens following transplantation often included the frequent administration of antacids to prevent ulcer occurrence. Antacids were often continued for months after transplantation and were reinstituted if rejection required increased steroid doses. Antacids have been supplanted by H_2-blockers during the last 15 years. Since 1983, the use of cyclosporine has permitted substantial decreases in steroid dosage, and the incidence of peptic ulceration in transplant recipients is now very low.[18] As a result, ulcer prophylaxis is not always routinely provided. A history of peptic ulcer disease documented by radiographs or endoscopy or prolonged use of high-dose steroids ($\geq$ 20 mg/d of prednisone) is now thought to be an indication for ulcer prophylaxis. Without specific signs or symptoms of peptic ulcer disease, the routine use of H_2-blockers or antacids should be avoided.

Hypertension

High blood pressure is a universal problem of transplant recipients; as many as 90 percent of renal transplant recipients and nearly 100 percent of patients receiving heart transplants will be hypertensive in the first few months following surgery.[36-38] The major contributor to postsurgical hypertension is probably cyclosporine-mediated release of endothelin, a potent vasoconstrictor.[39] Renal vasoconstriction causes sodium and water retention with intravascular volume expansion. Despite many case reports, personal prejudices, and suggestions in the literature, no one has consistently shown that one class of antihypertensive medications is more effective or more toxic in transplant recipients than any other class. On theoretic grounds, calcium channel blockers might protect the kidney from cyclosporine-induced nephrotoxocity, although whether in practice this protection occurs is not entirely clear.[40] If used during or immediately after the transplant procedure, calcium channel blockers might also prevent the development of ischemic and immunologically related cellular injury.[41-43] Again, this finding is more theoretic than practical. Many use calcium channel blockers, with or without the addition of diuretics, as the initial antihypertensive medication for the theoretic reasons listed above. In addition, verapamil, diltiazem, and probably nicardipine

partially inhibit cyclosporine catabolism, allowing the administration of lower cyclosporine doses to achieve the same serum levels. Nifedipine and isradipine do not affect cyclosporine catabolism. Because of the very high cost of cyclosporine ($4000 to $6000 per year), drugs that lower the requirement for this agent yield a substantial economic benefit to the transplant recipient. It should be noted that altering therapy with these drugs will alter cyclosporine levels and put the patient at risk for rejection or toxicity. Angiotensin-converting enzyme (ACE) inhibitors can cause hyperkalemia, acidosis, and worsening azotemia if renal artery stenosis or volume depletion is present. Attention to serum electrolytes can reveal these problems, so the potential danger of ACE inhibitors has probably been overemphasized. The selection of other antihypertensive medications is based on the usual considerations in any hypertensive patient. Severe hypertension, unresponsive or minimally responsive to high doses of several medications, should prompt a search for renal transplant artery stenosis or consideration of native nephrectomy.

Cyclosporine Levels

Cyclosporine is a mainstay of all current immunosuppressive protocols; a tremendous amount of time and money is spent measuring levels and adjusting dosage to achieve appropriate immunosuppression while minimizing nephrotoxicity and hypertension. There are three major problems commonly encountered. First, several different tests measure cyclosporine levels (e.g., radioimmunoassay, enzyme-linked immunosorbent assay, fluorescent polarization immunoassay, high-pressure liquid chromatography). They measure either the parent molecule or parent plus metabolites, and the level can be obtained from either whole blood or serum. Because the methods and targets differ, and because cyclosporine is very lipophilic and partitions selectively within cell membranes, the results from these tests are very different and are not comparable. It is therefore important that a patient have levels consistently measured by the same test at the same laboratory so that valid comparisons can be made and dosage adjusted. Second, the major pathway for cyclosporine catabolism is through the hepatic P450 system. Many commonly used drugs activate or inhibit P450 metabolism and can drastically alter cyclosporine blood levels. Many cases of cyclosporine nephrotoxicity or rejection are caused by medication changes. Commonly used medications that alter cyclosporine levels are listed in Table 8. Third, the relevant measurement of cyclosporine is a 12- or 24-hour trough level; measurements of random levels yield no useful data.

Hyperlipidemia

Hyperlipidemias are common among transplant recipients and have independent contributions from glucocorticoids and cyclosporine.[44] One of the major causes of long-term morbidity and mortality among transplant patients is cardiovascular disease.[18] Close attention should therefore be given to modifying diet, weight, total and low-density lipoprotein cholesterol levels, and hypertension in these patients. As with other groups, nutritional modification is probably the major component in controlling cardiovascular risks; however, dietary modification is often difficult because glucocorticoids increase appetite and weight gain. A reduction in glucocorticoid and cyclosporine doses, as warranted by allograft function, is another major element in controlling hyperlipidemia. Drug therapy for hyperlipidemia presents problems in the transplant population. Many lipid-lowering medications are expensive. For a group of patients already taking 3 to 10 other medications, including cyclosporine, the cost can be prohibitive. Cholestyramine and colestipol cause many intestinal side effects and interfere with the enterohepatic circulation of

Table 8. Common Medications That Cause Changes in Cyclosporine Blood Levels.

Medications That Increase Cyclosporine Levels	Medications That Decrease Cyclosporine Levels
Bromocriptine	Carbamazepine
Danazol	Phenobarbital
Diltiazem	Phenytoin
Erythromycin	Rifampin
Fluconazole	
Itraconazole	
Ketoconazole	
Metoclopramide	
Nicardipine	
Verapamil	

bile salts (and cyclosporine absorption) and therefore could alter cyclosporine levels. Niacin causes intestinal, neurologic, and hepatic side effects and often is not acceptable for transplant patients. Lovastatin has been associated with rhabdomyolysis in patients taking cyclosporine[45]; however, lovastatin has been used successfully in renal transplant recipients, though creatinine phosphokinase levels must be monitored closely. Pravastatin looks promising in initial studies; however, its cost might prevent widespread use.[46] Clofibrate and gemfibrozil are contraindicated in patients with renal or hepatic dysfunction. Probucol is contraindicated in patients with cardiac dysfunction and causes a high number of other side effects.

Hyperuricemia and Gout

Before the advent of cyclosporine, clinical gout in transplant recipients was extremely uncommon, perhaps because of the effects of steroids and azathioprine. Azathioprine is a weak inhibitor of, and is metabolized by, the xanthine oxidase system (see below) and thus decreases serum uric acid levels. Steroids are anti-inflammatory agents and can also lower the renal threshold for uric acid excretion. Because cyclosporine has been used for immunosuppression, hyperuricemia is common (an incidence of 85 percent was reported in one series), and clinical gout can occur in 4 to 24 percent of renal transplant patients.[47] Cyclosporine decreases the clearance and fractional excretion of uric acid.[48] The vasoconstriction induced by cyclosporine causes increased proximal reabsorption of uric acid. In addition, there might be a specific tubular defect in uric acid excretion caused by cyclosporine. A group of patients switched from cyclosporine to azathioprine therapy retained the defect in uric acid excretion long after the cyclosporine was gone.[47]

Asymptomatic hyperuricemia should not be treated because it is so common. If clinical gout is suspected, arthrocentesis should be performed, and the fluid examined and cultured. If gout is confirmed, its treatment can present problems (Table 9). All nonsteroidal anti-inflammatory drugs (NSAIDs) interfere with prostaglandin-dependent renal blood flow, causing a rise in serum creatinine levels. There is no evidence that NSAIDs cause permanent renal damage; the rise in creatinine level should reverse within a few days of stopping the NSAID. For this reason it is safe to prescribe NSAIDs for the treatment of acute gout in the transplant recipient who has stable renal function. Alternatively, or in patients who do not have stable renal function, acute gouty attacks can be treated with colchicine or with a short course of higher dose steroids.

Table 9. Treatment of Gout.

Symptom	Treatment
Asymptomatic hyperuricemia	Do not treat
Infrequent acute gouty attacks	NSAIDs* (must have stable renal function) Colchicine Glucocorticoids
Frequent acute gouty attacks	Long-term colchicine administration Long-term probenecid administration Consider allopurinol only if other measures fail. Must follow complete blood count closely and reduce azathioprine to 1/3 of previous dose.

*NSAID — nonsteroidal anti-inflammatory drug.

Occasional episodes of acute gout can be treated when they occur. If gouty attacks become frequent, ongoing therapy might be necessary. Some patients will respond to continuous administration of low-dose colchicine. Allopurinol should be avoided as first-line treatment and reserved only for refractory cases. Because azathioprine is metabolized by means of the xanthine oxidase pathway, the addition of allopurinol will increase the potency of azathioprine by a factor of two to three and result in overimmunosuppression and bone marrow suppression. Prescribing allopurinol for a patient taking azathioprine therefore requires that the dose of azathioprine be reduced to about one-third of previous levels. Even with this reduction, the white cell count should be monitored closely for a few weeks following initiation of allopurinol therapy.

Renal Insufficiency

Decreased renal function is ubiquitous in all recipient groups. Chronic low-flow states in cardiac failure induce permanent changes in kidney structure including nephron unit dropout. Chronic liver disease frequently induces permanent changes in renal function and structure through unknown mechanisms. For a well-functioning renal allograft, a serum creatinine of 1.2 to 1.6 mg/dL usually translates into a glomerular filtration rate < 50 mL/min. In practical terms any transplant

patient should be assumed to have renal insufficiency. Hypovolemia and nephrotoxic medications should be avoided, if possible; radiographic contrast dyes should be used with caution; and dosage of drugs excreted renally should be adjusted appropriately. In this context it is also important to note that both trimethoprim and cimetidine cause a rise in serum creatinine level, without truly changing renal function, by interfering with normal tubular secretion of creatinine. Tubular secretion of creatinine plays a larger role in creatinine excretion as renal function declines. This elevation is reversible when the drug is discontinued.

Gingival Hyperplasia

An important and often overlooked aspect of patient care is attention to oral hygiene. Both calcium channel blockers and cyclosporine are associated with gingival hyperplasia in up to 30 percent of patients. The combination of drugs can be additive or even synergistic in their effect on gingival tissue.[49] Attention to preexisting periodontal disease and good maintenance of oral hygiene are important for prevention. Extensive oral surgery and gingival excision might be necessary for florid cases.

Liver Function Abnormalities

Abnormalities of liver function tests are common in the transplant population; some series are reported as having an incidence of more than 60 percent.[50] In the liver transplant group, liver function test abnormalities can be due to rejection, infection, or technical complications. It is best that these possibilities be evaluated by the transplant center, especially after recent transplantation. In other transplant groups the causes of liver function test abnormalities are discussed below. Both azathioprine and cyclosporine have been associated with abnormalities in liver tests.[51] The abnormalities associated with azathioprine suggest an obstructive process. In a stable recipient in whom azathioprine is the suspected cause of liver dysfunction, the drug can be discontinued as long as the cyclosporine dose is adequate. If after 6 to 8 weeks the liver function abnormalities have resolved, the patient can be rechallenged with the drug. If the abnormalities have not resolved, then azathioprine was probably not the cause, and the patient can resume using the drug. With cyclosporine, the abnormality might be hepatitic but is usually cholestatic, causing increases in both alkaline phosphatase and bilirubin levels. The hepatic toxicity of cyclosporine is dose related; checking cyclosporine levels and lowering the dose of the drug will often yield resolution of the liver dysfunction. Other commonly used drugs might also cause liver dysfunction; these drugs include isoniazid, alpha-methyldopa, and phenothiazines.

The major cause of liver dysfunction following transplantation is viral hepatitis. In the immediate post-transplant period, acute hepatitis can be caused by CMV, EBV, or other herpesvirus infections. These diseases are usually self-limited and can be diagnosed and treated as described above. Hepatitis A usually causes no more problems in the transplant recipient than in other patients.

The prevalence of and morbidity from hepatitis B and C are under debate. Hepatitis B seropositive individuals are not used as organ donors; therefore, hepatitis B is not an issue in this group. Hepatitis C seropositive individuals were used as organ donors before the recently available tests for hepatitis C antibody, antigen, and RNA. Hepatitis C seems to have been transmitted to 100 percent of recipients receiving organs from infected donors, although the actual incidence of clinically important liver disease is disputed. Currently hepatitis C seropositive organs are used only for recipients expected to die of organ failure within 24 to 48 hours unless transplantation is performed.

For hepatitis B or C seropositive recipients, the incidence of progressive liver disease is also uncertain. A substantial number of kidney recipients could die of chronic liver disease many years after a successful transplant, although the precise number is unclear. It was originally thought that more than 50 percent of kidney transplant recipients carrying the hepatitis B virus would die of chronic liver disease 5 years or more after transplantation.[52] More recent studies suggest that chronic liver disease occurs in only about 10 percent of these patients.[53] In addition, the prevalence of hepatitis B in the transplant population is falling as a result of routine blood screening for the virus, vaccination, and the use of erythropoietin in limiting transfusions.

With the recent availability of screening for hepatitis C, there have been many reports of disease prevalence. Prevalence in dialysis and transplant populations varies from 10 percent to more

than 50 percent, correlating with the length of time on dialysis and the number of transfusions received.[54] The long-term outcome of recipients carrying this virus remains to be determined, although the post-transplant course is in general benign. It is currently considered appropriate to perform renal, pancreas, or heart transplants in hepatitis B or C seropositive recipients who have stable hepatic function and are without evidence of progressive liver disease.

Liver transplantation in these recipients is more controversial. Hepatitis B will recur in 100 percent of recipients, and at least 50 percent will experience progressive liver disease as a result of the virus.[55] Although hepatitis C will probably recur in 100 percent of recipients, the incidence of major or progressive viral disease is unknown but is probably under 50 percent.[56] Currently hepatitis B is an important relative contraindication to transplantation, whereas hepatitis C is considered a minor relative contraindication. As the biological processes of these viruses and diseases are further elucidated and as interventions to alter their natural history become available, these recommendations might change.

A patient with persistent abnormalities of liver function should be examined by a hepatologist, and consideration should be given to a liver biopsy. It is also worth noting that a common source of elevated alkaline phosphatase levels in patients with chronic kidney or liver disease can result from bone, not liver, disease.

Hypercalcemia

Hypercalcemia after renal transplantation occurs in up to 30 percent of recipients as a result of hyperplasia of the parathyroid glands. The abnormalities present during uremia that cause parathyroid hyperplasia — phosphate retention, failure of activation of vitamin D, and resistance to parathyroid hormone (PTH) action — disappear rapidly when the patient receives a functioning kidney, whereas resolution of hyperplasia lags behind. Seventy percent of cases of hypercalcemia resolve spontaneously during the first 12 months, while 25 percent of patients have persistent, asymptomatic, borderline hypercalcemia with levels less than 11.5–12.0 mg/dL. The remaining 5 percent of patients eventually require parathyroidectomy because calcium levels consistently exceed 12 mg/dL or they show symptoms of hypercalcemia.[57] Asymptomatic elevation of calcium and PTH levels in the early post-transplant period should therefore be monitored for at least 12 months before considering parathyroidectomy. While both calcium and PTH levels are important for diagnosis, the criterion for parathyroidectomy is the calcium level. PTH levels are often elevated in recipients who have excellent renal function and normal calcium levels and cannot be the basis for a decision regarding surgery. This elevation in PTH is probably due to the residual renal insufficiency, as well as parathyroid hyperplasia, present in all renal recipients. The recommended surgical procedure is now four-gland removal plus autotransplantation of an appropriate amount of tissue to the sternocleidomastoid or forearm muscles.

Bone Disease

Long-standing renal and hepatic disease often results in osteomalacia or osteoporosis. Following a transplant, because many metabolic abnormalities are normalized, patients might require large doses of vitamin D and calcium to help restore proper bone mass and mineralization, particularly in hepatic transplant patients who had biliary obstructive diseases in which there was long-term malabsorption of fat-soluble vitamin D.

Hematologic Problems

Erythrocytosis with hematocrit levels greater than 55 percent occurs in 10 to 15 percent of renal transplant recipients.[58] It appears to result from the continued secretion of erythropoietin by the native kidneys that has escaped from the normal feedback mechanisms.[59] Although erythrocytosis can be cured by bilateral native nephrectomy, most cases are managed by periodic phlebotomy (without iron therapy), because the condition seems to resolve with time, perhaps as the native kidneys are gradually obliterated. A recent report suggests that erythrocytosis will respond to the administration of theophylline.[60]

Azathioprine causes macrocytosis by blocking folate metabolism; the macrocytosis cannot be reversed by administration of folic acid. Macrocytosis occurs in virtually all patients taking azathioprine and requires no investigation; mean corpuscular volume (MCV) levels greater than 110 μm^3 are not unusual. In fact, a patient taking azathioprine who has a normal MCV might be

iron deficient, which can be supported by check of the corpuscular red cell distribution width.

Finally, few patients will show a persistent leukocytosis, with a cell count usually in the range of 12,000 to 20,000 μm^3. The cause is not known, although it could be due to either persistent demargination of white cells from steroid therapy or disordered leukocyte trafficking induced by the immunosuppressive drugs. It is not unusual to see both leukocytosis and thrombocytosis during the period of marrow recovery following successful renal transplantation.

Psychosocial Issues

The dependency on the function of a foreign organ and the rapidity with which patients can become well after transplantation or deteriorate when an organ fails create a series of unique problems. High-dose steroids can induce euphoria and mania, and a rapid steroid taper can be associated with depression. Fortunately these side effects are uncommon, transient, and take place almost solely in an inpatient setting.

Most patients derive substantial benefit from their organs and report enhanced well-being, quality-of-life indicators, and ability to work, and they can attend school and participate in normal activities. Within this group of patients two types of problems can be anticipated. The first, noncompliance with medications, occurs particularly among adolescents and is associated with notions of invulnerability, which are common in adolescents, and with the desire to avoid cosmetically undesirable side effects of immunosuppression, e.g., acne and Cushingoid facies from glucocorticoids.

A second problem is divorce, which might occur soon after a successful transplant. The healthy spouse has often been consumed by care of the sick spouse. When transplantation enables the recipient to resume normal activities, the healthy spouse might choose to disengage and concentrate on his or her own life, before the recipient has a chance to develop any complications from the procedure. The healthy spouse also might feel relatively free of guilt about divorce because the recipient is now "well." A variation of this scenario is that the recipient no longer must be dependent on the healthy spouse. The roles of caregiver and dependent have been usurped, and one or both parties might find their new roles untenable.[61]

Transplant patients and their families face severe financial stress. The most common problem is inability to pay for expensive immunosuppressive medications. For example cyclosporine can cost up to $12,000 per year. This cost leads to episodes in which the patient discontinues immunosuppression and suffers subsequent graft loss with resulting morbidity and mortality. The patchwork of federal, state, and private methods of payment are usually successful in helping most patients. It is important for patients to plan well into the future how they will pay for medications. Consultation with the transplant center and coordination with local social service resources are important, because the center is likely to have the most information about and access to available resources.

Summary

The growth and success of transplantation assures that increasing numbers of transplant recipients will seek care from generalist, primary care physicians. It will be important for these physicians to be aware of potential problems and complications that are unique to the transplanted organ and to the immunosuppressive medical regimen. Likewise, knowledge of common myths, misconceptions, presentations, and problems will enhance the ability to diagnose and treat these patients. The ultimate mainstay of care is consultation with the patient's transplant center at an early stage of problem formation to create a care plan and to transfer the patient to the center if the condition necessitates such action.

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