Medical Complications of Renal Transplantation

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With long-term function of allografts increasingly the norm, detection and management of medical complications assume greater importance in the care of renal transplantation recipients. At least two trends in transplantation seem likely to make medical surveillance even more crucial. First, better control of adverse immunologic events early after transplantation has significantly reduced graft loss caused by rejection; the impact of later events (especially death with a functioning organ and chronic rejection) on graft and patient survival is proportionately larger. Second, with successful transplantation now fairly routine, it is being offered to a broader spectrum of candidates, including increasingly older patients with multiple coexisting medical problems. Because more patients with immunosuppression are now being cared for over increasingly longer periods of time, the impact of comorbid events on outcomes must be reduced.

Medical complications in the renal allograft recipient represent the often overlapping impact of several variables. At the time of transplantation, significant comorbidity may already be present and can be of immediate concern. Other problems may have originated in the milieu of chronic renal failure, such as hyperparathyroid bone disease or hypertension, but may evolve differently after transplantation. Finally, new complications may result from specific toxicities of pharmaceutical agents, reflecting the overall impact of immunosuppression. In many cases, all of these elements contribute to overt clinical illness. For instance, cardiovascular disease is now the most common cause of death in renal allograft recipients [1]. Coronary disease may have predated transplantation (indeed, coronary disease is a common cause of death among all patients with end-stage renal disease). After transplantation, hypertension and hyperlipidemia, perhaps exacerbated by administration of cyclosporine and corticosteroids, result in accelerated atherosclerosis, further potentiating preexisting cardiac problems. To intervene appropriately requires a comprehensive understanding of all the variables involved: any decision to lessen the impact of one risk factor (*eg*, withdrawing steroids) may result in unintended consequences (*eg*, acute rejection).

CHAPTER

13

An obvious prerequisite to caring for transplant recipients is a thorough understanding of immunosuppressive therapies [2]. Although acute rejection can occur at any time, the greatest risk is during the first 90 days after transplantation. Accordingly, immunosuppression is most intense during this time, and the chances of suffering its consequences are great (*eg*, drug toxicities, infection, and some malignancies [lymphoma]). In general, tapering to a less arduous regimen over time is done, with resulting reduction in the risks of toxicity and infection. With long-term survival, however, the duration rather than the intensity of immunosuppression becomes more critical and strongly influences the risks of other complications, including malignancies (skin), bone disease, and atherosclerosis.

Current maintenance immunosuppressive therapy involves multidrug regimens (including azathioprine or mycophenolate mofetil [MMF] and corticosteroids) built around a cornerstone, the calcineurin-inhibitor (either cyclosporine or tacrolimus) [2]. Therapeutic considerations in treating patients on either of the calcineurin inhibitors are remarkably similar in terms of both adverse effects and drug interactions (Figs. 13-1 and 13-2) [3–5]. Common azathioprine toxicities include bone marrow suppression and alopecia. Because azathioprine is metabolized by xanthine oxidase, concomitant use with allopurinol is problematic. MMF causes less bone marrow suppression than does azathioprine and does not interact with allopurinol, facilitating therapy of gout. However, gastrointestinal complaints (usually dose-related nausea, bloating, or diarrhea) are common. In addition, MMF may exacerbate the gastrointestinal toxicity of tacrolimus. Corticosteroid toxicities are well described; protocols designed to minimize corticosteroid exposure of transplantation recipients remain the ideal pursued by many physicians who treat these patients.

ADVERSE EFFECTS OF CYCLOSPORINE AND TACROLIMUS

Renal	Gastrointestinal	Metabolic	Cosmetic	Neurologic
Hypertension	Hepatotoxicity (abnormal	Glucose intolerance (FK > CyA)	Gingival hypertrophy	Headache
Nephrotoxicity	transaminase levels)	Hyperkalemia	(CyA only, especially	Paresthesias
(azotemia)	Nausea, vomiting, diarrhea	Hyperlipidemia (CyA > FK)	in combination with	Seizures
	(FK > CyA)	Hyperuricemia	calcium antagonists)	Tremor
		Hypomagnesemia	Hirsutism (CyA > FK)	

FIGURE 13-1

Despite differing structures, both cyclosporine and tacrolimus bind to intracellular receptors in T cells, forming a combination that then inhibits calcineurin-dependent pathways of cell activation. Although slight differences exist in side-effect profiles between the two drugs, their overall impact is remarkably similar. In many cases, dose reduction may ameliorate the toxic effect; however, the benefit of dose reduction must be weighed against increasing the risk of acute rejection in each patient. CyA–cyclosporine; FK–tacrolimus.

COMMON DRUG INTERACTIONS WITH CYTOKINE INHIBITORS

Drugs that commonly increase blood levels of cyclosporine and tacrolimus
  Bromocryptine
  Cimetidine
  Clarithromycin
  Clotrimazole
  Diltiazem
  Erythromycin
  Fluconazole
  Itraconazole
  Ketoconazole
  Mefredil
  Methylprednisolone
  Nicardipine
  Verapamil
Drugs that commonly decrease blood levels of cyclosporine and tacrolimus
  Carbamazepine
  Phenobarbital
  Phenytoin
  Rifampin

FIGURE 13-2

Cyclosporine and tacrolimus are subject to remarkably similar interactions, owing in part to a common pathway of metabolic degradation, the cytochrome P-450 enzyme system. Although the drugs listed here predictably alter blood levels of the calcineurin inhibitors, other interactions may also occur.
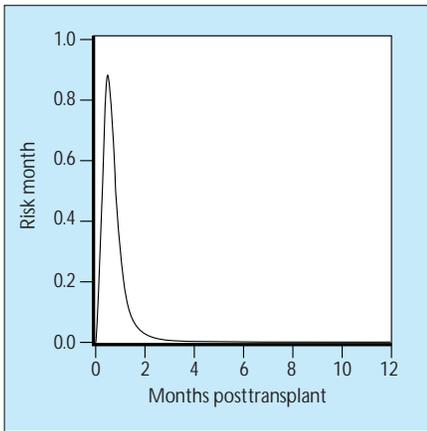
FIGURE 13-3

Risk of acute rejection in cadaver kidney transplantation. This graph, derived from the parametric analysis techniques of Blackstone and coworkers [6], depicts the risk of acute rejection over time. Using an immunosuppressive protocol including cyclosporine, mycophenolate mofetil, and prednisone, the risk of acute rejection is greatest during the first 2 months after transplantation, diminishing significantly afterward. Because the risk of rejection is greatest, immunosuppressive therapy is most intense during this period. Correspondingly, complications related to immunosuppressive therapy (including infections and specific drug toxicities) also are most likely during this time.
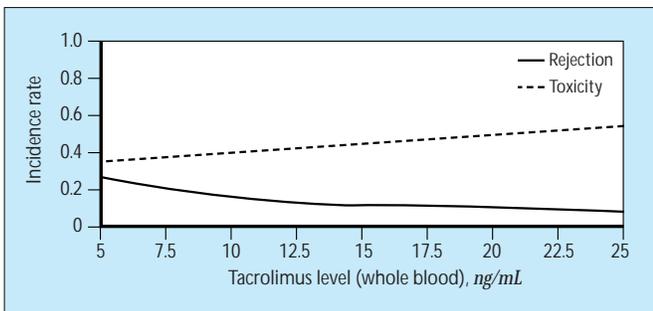
FIGURE 13-4

Relationship between blood levels of tacrolimus, immunosuppressive efficacy, and toxicity [7]. As tacrolimus levels diminish, particularly during the early period after transplantation, the risk of toxicity is reduced accordingly. However, the risk of acute rejection increases. Toxicity still can occur at very low drug levels, as can rejection at high levels. The relationship between these variables beyond the first 6 to 12 months after transplantation is not well established. A similar plot could be constructed for cyclosporine. (*Adapted from* Kershner and Fitzsimmons [7].)

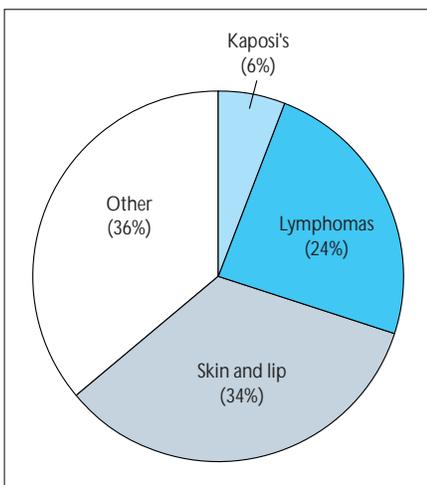# Complications of Immunosuppression

Malignancy

FIGURE 13-5

Types and distribution of malignancies among renal transplant recipients in the current era of cyclosporine use. In these patients the risk of malignancy is increased approximately fourfold when compared with the general population [8]. Malignancies likely to be encountered in the transplantation recipient differ from those most common in the general population [9,10]. Lymphomas and Kaposi's sarcoma may evolve as a consequence of viral infections. Women are at an increased risk for cervical carcinoma, again related to infection (human papilloma virus). Surprisingly, the solid tumors most commonly seen in the general population (*eg*, of the breast, lung, colon, and prostate) do not occur with significantly greater frequency among transplant recipients. Nonetheless, long-term care of these patients should involve standard screening for these malignancies at appropriate intervals. (*From* Penn [9]; with permission.)

FIGURE 13-6

Primary basal cell carcinoma. Cutaneous carcinomas (primarily basal cell and squamous cell) comprise the greatest percentage of tumors in transplant recipients. They tend to be most problematic in fair-skinned persons whose lifestyle includes significant sun exposure; the risk increases with duration of immunosuppression. In immunocompetent patients the risks of these lesions usually are limited; however, in transplant recipients these lesions can be very aggressive and metastasize locally or even systemically. The best management is aggressive prevention: exposure to ultraviolet radiation from the sun should be minimized through diligent use of protective clothing, hats, and sunscreen. When suspicious lesions develop, early recognition and removal are of utmost importance.
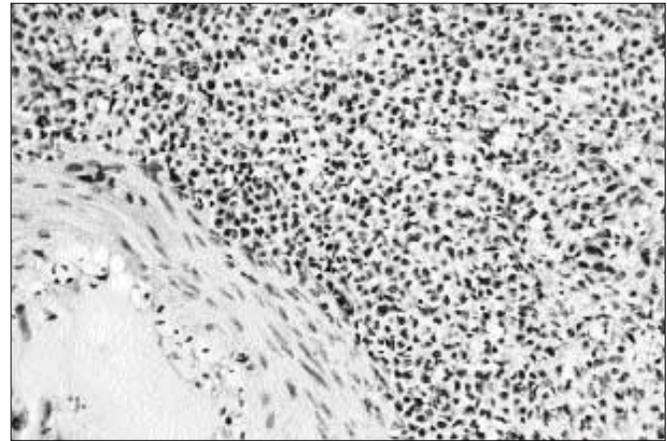

FIGURE 13-7

Posttransplantation lymphoproliferative disease (PTLD): histologic appearance of a renal allograft infiltrated by a monoclonal proliferation of B lymphocytes. Non-Hodgkin's lymphomas, of which PTLD is a variant, occur in 1% to 3% of transplant recipients and in many cases are linked to an infectious cause. PTLD can be of either polyclonal or monoclonal B-cell composition, with lymphocytes driven to proliferate by infection with the Epstein-Barr virus [11–13]. Development of PTLD is strongly linked to the intensity of immunosuppression and may regress with its reduction. However, most often in the setting of splanchnic involvement and monoclonal proliferation, as depicted, PTLD can follow a more aggressive unrelenting course despite withdrawal of immunosuppressive therapy.
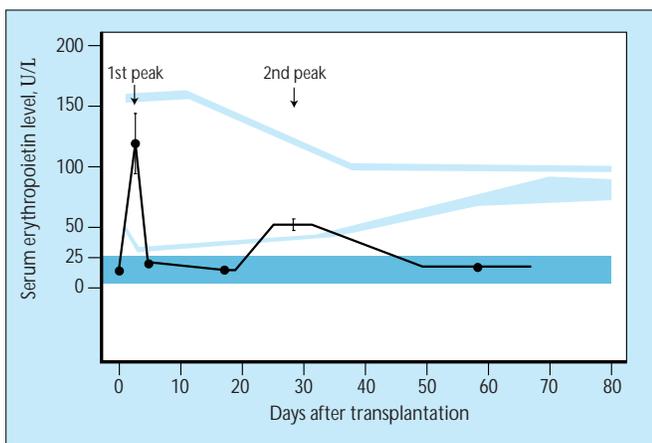
Hematologic Complications

FIGURE 13-8

The course of normal erythropoiesis after renal transplantation showing mean serum erythropoietin levels of 31 recipients [14]. An initial burst of erythropoietin (EPO) secretion at the time of engraftment does not result in erythropoiesis. As excellent graft function is achieved, a second burst of EPO secretion is normally followed by effective production of erythrocytes. The hatched area is the range of serum erythropoietin levels in normal persons without anemia.

Anemia is a common complication. Many patients leave the dialysis population with diminished iron stores and are unable to respond to erythropoietin produced by the successful allograft. Iron replacement therapy successfully restores erythropoiesis in these patients. Another common cause of anemia after transplantation is bone marrow suppression owing to drug therapy with azathioprine or mycophenolate mofetil (MMF), an effect that is usually dose-related [15,16]. Other drugs, notably angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists, may also inhibit erythropoiesis [17].

Neutropenia also is a common complication after transplantation. It can reflect dose-related bone marrow suppression owing to drug therapy with azathioprine or MMF or an idiosyncratic response to a number of drugs commonly used in this population (acyclovir, ganciclovir, sulfa-trimethoprim, H_2 blockers). Alternatively, neutropenia can be a manifestation of systemic viral, fungal, or tubercular infections. The approach to the patient with neutropenia usually involves reducing the dose or discontinuing the potential offending agents, along with a careful search for infections. In some settings of refractory neutropenia, administration of filgrastim (granulocyte colony-stimulating factor, Neupogen®) reduces the duration and severity of neutropenia. (*From* Sun and coworkers [14]; with permission.)
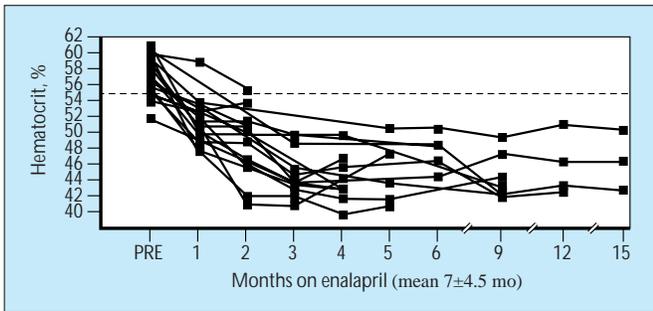
FIGURE 13-9

Posttransplant erythrocytosis (PTE). PTE (a hematocrit of >0.52) affects 5% to 10% of renal transplantrecipients, most commonly male recipients with excellent allograft function [17]. PTE usually occurs during the first year after transplantation. Although it may resolve spontaneously in some patients, PTE persists in many. It has been linked to an increased risk of thromboembolic events; however, our own experience is that such events are uncommon. Previous management involved serial phlebotomy to maintain the hematocrit at 0.55 or less (*dashed line*). More recently, hematocrit levels have been found to normalize in almost all affected patients with a small daily dose of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor antagonist. The pathogenetic mechanisms underlying PTE and its response to these therapies remain poorly understood; although elevated serum erythropoietin levels decrease with ACEI use, other pathways also appear to be involved.

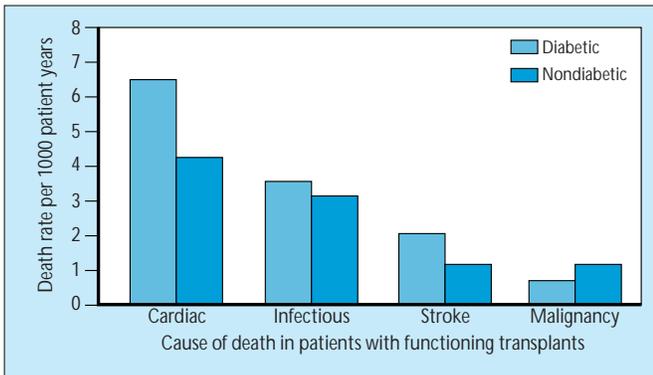# Cardiovascular Complications

FIGURE 13-10

Causes of death in renal allograft recipients. Cardiovascular diseases are the most common cause of death, largely reflecting the high prevalence of coronary artery disease in this population [1]. The risks are particularly high among recipients who have diabetes, as many as 50% of whom, even if asymptomatic, may have significant coronary disease at the time of transplantation evaluation [18]. Effective management of cardiac disease after transplantation mandates documentation of preexisting disease in patients at greatest risk [19].

DEMOGRAPHIC VARIABLES HIGHLY PREDICTIVE OF CORONARY DISEASE IN RENAL TRANSPLANTATION CANDIDATES WITH INSULIN-DEPENDENT DIABETES MELLITUS

Age > 45 y
Electrocardiographic abnormality: nonspecific ST-T wave changes
History of cigarette smoking
Duration of diabetes > 25 y

FIGURE 13-11

Demographic variables highly predictive of coronary disease in renal transplantation candidates with insulin-dependent diabetes mellitus. Most transplant centers screen potential candidates, particularly persons with diabetes, for coronary disease before transplantation. In patients with diabetes who have end-stage renal disease with none of the demographic characteristics listed, the risk for coronary disease is low. Conversely, in patients who are insulin-dependent and have any of these risk factors, the prevalence of coronary disease is sufficiently high to justify angiography. A randomized study of medical therapy versus revascularization in transplantation candidates who have insulin-dependent diabetes and coronary disease showed superior outcomes with prophylactic revascularization, even in the absence of overt symptomatology [20]. (*Adapted from* Manske and coworkers [18].)
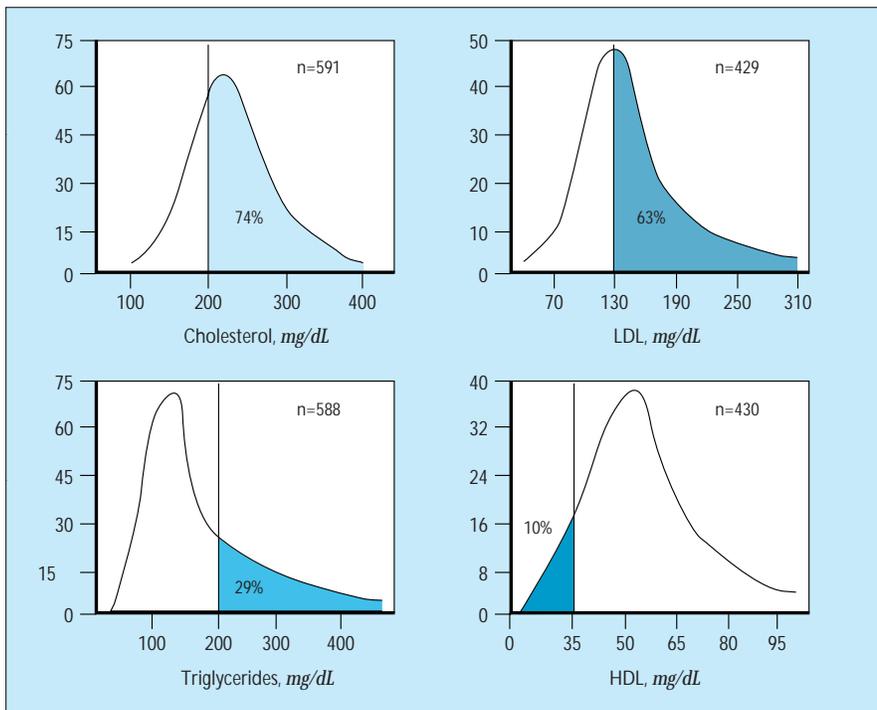
FIGURE 13-12

Hypercholesterolemia and hypertriglyceridemia. Hypercholesterolemia and hypertriglyceridemia are common after kidney transplantation. Approximately two thirds of transplant recipients have low density lipoprotein (LDL) or total cholesterol levels signifying increased cardiac risk; 29% have elevated triglyceride levels 2 years after transplantation (Kasiske, Unpublished data). Not only is hyperlipidemia a clear risk factor for coronary disease (*see* Figs. 13-13 and 13-14), but it may also contribute to the progressive graft dysfunction associated with chronic rejection [21,22]. HDL—high density lipoprotein. (*From* Bristol-Myers Squibb [23]; with permission.)

RISK FACTORS FOR CORONARY MORBIDITY IN RENAL ALLOGRAFT RECIPIENTS

Positive	Negative
Age:	HDL cholesterol ≥ 60 mg/dL
Male ≥ 45 y	
Female ≥ 55 y or premature menopause	
Family history of premature coronary heart disease	
Smoking	
Hypertension	
HDL cholesterol < 35 mg/dL	
Diabetes mellitus	

FIGURE 13-13

Risk factors for coronary morbidity in renal allograft recipients. In addition to elevated low density lipoprotein (LDL) cholesterol levels, risk factors known to contribute to coronary morbidity often are present in renal allograft recipients. About 40% of recipients are over 45 years old, and 23% have diabetes. Smoking, hypertension, and hyperlipidemia are among the risk factors most amenable to long-term modification. (For guidelines in instituting lipid-lowering therapy see Figure 13-14 [24].)

GUIDELINES FOR LIPID-LOWERING THERAPY

LDL cholesterol, mg/dL	Diet therapy	
	Initiation	Goal
No CHD and <2 risk factors	≥160	<160
No CHD and ≥2 risk factors	≥130	<130
CHD	≥100	≤100
LDL cholesterol, mg/dL	**Diet plus drug therapy**	
	Initiation	Goal
No CHD and <2 risk factors	≥190	<160
No CHD and ≥2 risk factors	≥160	<130
CHD	≥130	≤100

FIGURE 13-14

The indications for lipid-lowering therapy and its goals are based on the clinical history, risk factor profile (*see* Fig. 13-13), and low density lipoprotein (LDL) cholesterol level in individual patients. CHD—coronary heat disease. (*From* Grundy [24]; with permission.)
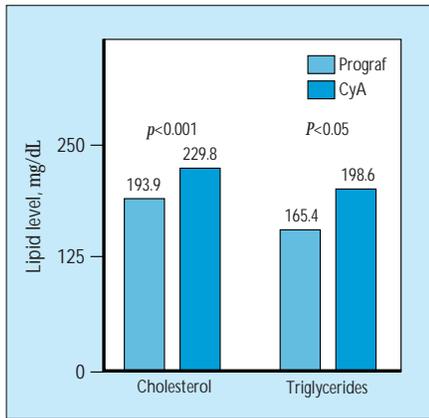
FIGURE 13-15

Cyclosporine (CyA) and corticosteroid therapies clearly contribute to hyperlipidemia in renal allograft recipients. Although dose reduction can reduce lipid levels, it may also increase the risk of acute rejection. As depicted, early experience in a large multicenter trial indicates that tacrolimus may have a less adverse impact on lipid metabolism than does cyclosporine [25]. (*From* Fujisawa USA [26]; with permission.)

THERAPEUTIC OPTIONS IN LIPID-LOWERING THERAPY

	HDL cholesterol	Cholesterol	LDL cholesterol	Triglycerides
Control groups	1±11	1±6	-15±22	2±4
Diet	-28±14	-21±15	-59±25	5±8
HMG CoA inhibitors	-56±9	-51±6	-49±18	3.5±4.5
Fibrates	-38±12	-36±9	-69±24	3±6
Fish oil	23±43		-86±80	
Probucol	-66±21	-49		-13.5±12
Niacin	-48±28			10±10

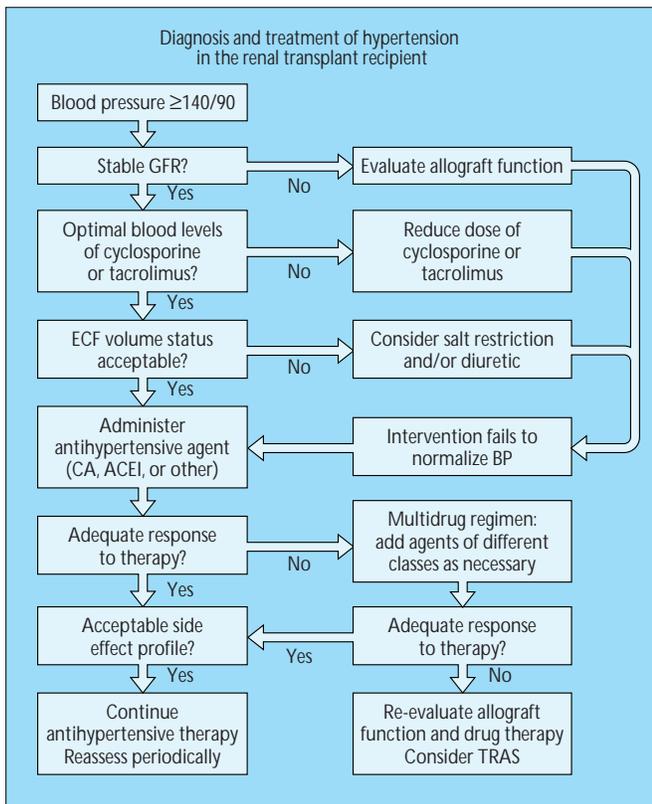mg/dL changes ±95% CI.

FIGURE 13-16

A recent meta-analysis of published trials in renal transplant recipients demonstrated these benefits of the various treatments. Pharmacologic therapy should be instituted at low doses with cautious surveillance for potential adverse effects, especially liver dysfunction or rhabdomyolysis. These adverse events may occur more frequently in transplant recipients owing to the effect of cyclosporine on drug disposition. Levels of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors are substantially higher in patients receiving both drugs [27]. HDL—high density lipoprotein; LDL—low density lipoprotein. (*Adapted from* Massy and coworkers [27]; with permission.)

CAUSES OF HYPERTENSION AFTER TRANSPLANTATION

Intrinsic	Extrinsic
Delayed graft function	Native kidneys
Acute rejection	Immunosuppression:
Chronic rejection	Cyclosporine
Cyclosporine nephropathy, chronic	Tacrolimus
Recurrent primary renal disease	Corticosteroids
(glomerulonephritis, hemolytic uremic	Transplantation renal artery stenosis
syndrome, and so on)	Hypercalcemia

FIGURE 13-17

In the current era of immunosuppressive therapy, hypertension affects roughly two thirds of transplant recipients. Unlike hypertension in the general population, posttransplant hypertension often reflects the impact of readily definable (and potentially treatable) factors on systemic blood pressure [28–30]. These may be grouped conveniently into those originating within the allograft (intrinsic) and those originating elsewhere (extrinsic).

Diagnosis and treatment of hypertension
in the renal transplant recipient

Blood pressure ≥140/90

Stable GFR? → No → Evaluate allograft function

Yes

Optimal blood levels of cyclosporine or tacrolimus? → No → Reduce dose of cyclosporine or tacrolimus

Yes

ECF volume status acceptable? → No → Consider salt restriction and/or diuretic

Yes

Administer antihypertensive agent (CA, ACEI, or other) ← Intervention fails to normalize BP

Adequate response to therapy? → No → Multidrug regimen: add agents of different classes as necessary

Yes

Acceptable side effect profile? ← Yes ← Adequate response to therapy?

Yes   No

Continue antihypertensive therapy Reassess periodically   Re-evaluate allograft function and drug therapy Consider TRAS

FIGURE 13-18

Hypertension in the renal transplant recipient. In these patients it may be possible to approach diagnosis and therapy in a fairly standardized fashion. In transplant recipients with blood pressure readings consistently over 140/90 mm Hg, intervention is warranted. The initial approach includes assessment of allograft function, extracellular fluid volume (ECF) status, and immunosuppressive dosing. If these variables are stable, it is reasonable to proceed with antihypertensive therapy. Calcium antagonists (CA) are effective agents and may offer the added benefit of attenuating cyclosporine-induced changes in renal hemodynamics. Verapamil, diltiazem, nicardipine, and mibefradil increase blood levels of cyclosporine and tacrolimus and should be used with caution. Common problems with CAs that may limit their use include cost, refractory edema, and gingival hyperplasia. Angiotensin antagonists (ACEIs and receptor antagonists) are also effective; their use requires close monitoring of renal function, serum potassium levels, and hematocrit levels. Diuretics frequently are useful adjuncts to therapy in recipients owing to the salt retention that often accompanies cyclosporine use. Other antihypertensive medications offer no particular benefits or drawbacks and can be employed as needed. The rationale of multidrug therapy is to employ agents that block hypertensive responses via interruption of differing pathogenetic pathways. As antihypertensive drugs are added, this consideration should remain paramount [31,32]. GFR—glomerular filtration rate; TRAS—transplanted renal artery stenosis.

FIGURE 13-19

Transplant renal artery stenosis (TRAS). TRAS accounts for less than 5% of cases of hypertension after transplantation. Nonetheless, TRAS should always be considered in patients with refractory hypertension who develop renal insufficiency after addition of an ACEI to the therapeutic regimen. Although noninvasive studies (such as a renal scan with captopril) may be helpful in diagnosing TRAS, angiography remains the gold standard for diagnosis. Revascularization of the allograft by either surgical or angioplastic techniques may improve renal function and ameliorate hypertension [33,34].

Gastrointestinal Complications

GASTROINTESTINAL TRACT COMPLICATIONS IN RENAL TRANSPLANTATION RECIPIENTS

Drug	Nausea and vomiting	Diarrhea	Other complications
Cyclosporine	4	3	Hepatotoxicity, constipation
Tacrolimus	30	32	Hepatotoxicity, constipation
MMF	20	31	Constipation, dyspepsia
Azathioprine	12	Rare	Hepatotoxicity, pancreatitis

FIGURE 13-20

Complications affecting the gastrointestinal (GI) tract remain relatively common in transplant recipients. Both tacrolimus and mycophenolate mofetil (MMF) cause bloating, nausea, vomiting, and diarrhea in a dose-dependent manner, particularly when used in combination [15,16,25]. Some authors have noted that this rather nonspecific GI toxicity occurs more commonly with Neoral® than with Sandimmune® (both from Sandoz Pharmaceuticals, East Hanover, NJ).

FIGURE 13-21 (*See* Color Plate)

Endoscopic image of candida esophagitis with diffuse white exudate (*panel A*) and colitis induced by cytomegalovirus infection with submucosal hemorrhage, ulcers, and diffuse mucosal edema (*panel B*). The availability and common use of effective prophylaxis against acid-peptic disease (*eg,* H_2 blockers, omeprazole, and antacids) have significantly reduced the frequency of upper gastrointestinal bleeding. However, infectious agents such as cytomegalovirus and candida continue to be problematic, particularly in the setting of the more intense immunosuppression afforded by drugs such as mycophenolate mofetil (MMF) and tacrolimus.
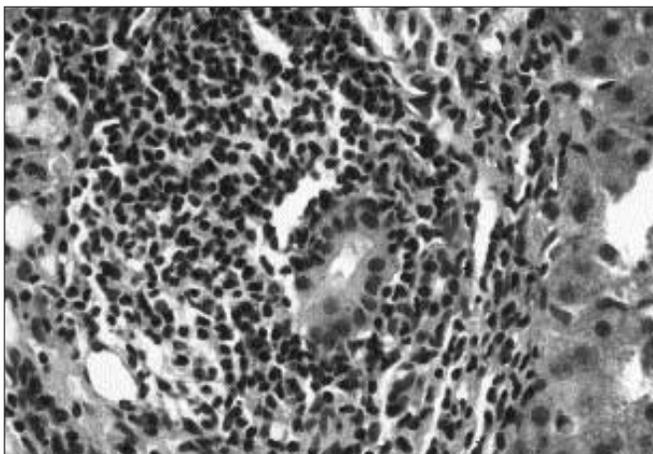
FIGURE 13-22

Histologic image of chronic active hepatitis secondary to infection with the hepatitis C virus (HCV). Note the periportal distribution of the lymphocytic infiltrate. Recent identification of HCV has caused intense reevaluation of the causes, frequency, and natural history of liver disease in renal allograft recipients. As the percentage of patients with end-stage renal disease who are infected with the hepatitis B virus has diminished, HCV has become the most problematic cause of liver disease. In recipients with HCV antibodies, immunosuppressive therapy may potentiate liver injury from the virus and accelerate the course of time over which cirrhosis develops. Nonetheless, in patients who desire transplantation and have well-preserved liver function, little evidence exists of better longevity on dialysis. HCV can be transmitted easily from donor to recipient in solid organ transplantation. Because kidney transplantation is not a life-saving procedure, most transplant centers choose not to use kidneys from donors who are infected with HCV.

Previously, liver disease was thought to be a common cause of death in renal allograft recipients. As blood transfusions have become less common in the dialysis population and hepatitis B virus less prevalent, the risk of death owing to hepatic disease seems to have diminished. Unfortunately, therapies for HCV-related hepatitis (interferon-α) have proved to be of questionable efficacy and may stimulate rejection of the renal allograft [35–37].

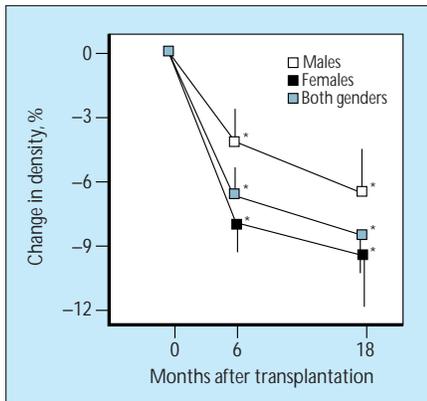# Musculoskeletal and Metabolic Complications

FIGURE 13-23

Mean percentage changes in bone mineral density of the lumbar spine after transplantation. Substantial bone loss can occur quite early after transplantation. Metabolic bone disease in this setting is usually multifactorial. Most often, patients who had end-stage renal disease before transplantation already have some degree of renal osteodystrophy, exacerbated in some cases by the impact of aluminum toxicity or β_2-microglobulin amyloidosis. Patients with diabetes are particularly at risk for low-turnover bone disease. Administration of corticosteroids and cyclosporine also contributes to bone loss. Although biochemical evidence of secondary hyperparathyroidism usually resolves during the first year after transplantation, some patients may have persistent parathyroid-driven bone resorption, with or without hypercalcemia, and may require surgical parathyroidectomy. Asterisk—values significantly different from those at the time of transplantation. (*From* Julian and coworkers [38]; with permission.)
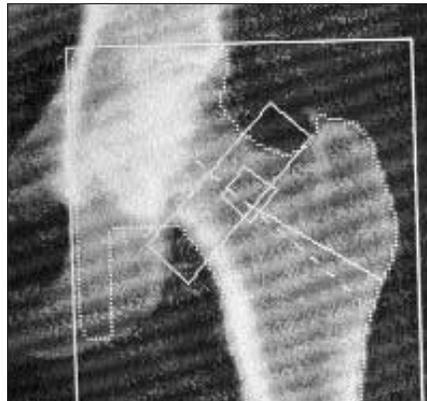

FIGURE 13-24

Bone densitometry. Bone densitometry offers a noninvasive method to quantitate bone mass. Here, a renal transplant recipient demonstrates marked osteoporosis, with bone density greater than 2 standard deviations below age- and gender-matched controls. In recent years, new therapeutic options (including bisphosphonates, estrogens, and thiazides) have offered hope of preserving or even increasing bone mass [38,39]. BMD—bone mass density.

FIGURE 13-25

Magnetic resonance imaging of osteonecrosis. Osteonecrosis most commonly affects the femoral head but can affect any weight-bearing bone. The most debilitating complication of renal transplantation, its incidence seems to be decreasing (<10% of transplant recipients). This decrease reflects better management of calcium and bone homeostasis during long-term dialysis and less intense steroid use after transplantation. The pathogenesis of osteonecrosis remains poorly understood, and therapeutic options are limited (pain management while awaiting progression to the need for joint replacement). Magnetic resonance imaging is a sensitive diagnostic method, allowing detection of osteonecrosis at a very early stage [39].

FIGURE 13-26

Photograph of gouty inflammation of joints (tophus). Gout is the clinical manifestation of hyperuricemia. After transplantation, cyclosporine can exacerbate hyperuricemia, and severe gout can be problematic even in the presence of chronic immunosuppression. Management of gouty arthritis usually involves some combination of colchicine and judicious use of short courses of nonsteroidal anti-inflammatory drugs. Concomitant administration of allopurinol and azathioprine can cause profound bone marrow suppression and is avoided by most physicians who treat transplant recipients. Because the metabolism of mycophenolate mofetil (MMF) is not dependent on xanthine oxidase, use of allopurinol in patients treated with MMF is relatively safe [39,40].

FIGURE 13-27

Photograph of gingival hyperplasia. Gingival hyperplasia occurs in approximately 10% of transplant recipients treated with cyclosporine. Its severity reflects the interaction of effective dental hygiene, cyclosporine dose, and concomitant administration of calcium antagonists (particularly dihydropyridines). This complication does not seem to occur with use of tacrolimus, and complete resolution of gingival hyperplasia has been noted with conversion from cyclosporine-based therapy [25,41].

INCIDENCE OF POST-TRANSPLANT DIABETES MELLITUS

PTDM (defined as requiring insulin $\geq$ 30 d)					
	Prograf * (n=151)		CyA (n=151)		
	n	%	n	%	P value
Initial	30	15.9	8	4.0	>0.001
At 1 year	25	18.5	5	3.3	>0.001
At 18 mo	18	12.0	0	3.3	

*Patients without history of diabetes.

FIGURE 13-28

Post-transplantation diabetes mellitus (PTDM). PTDM complicates the course of treatment in 5% to 10% of patients on cyclosporine-based immunosuppressive therapy. It is more common in blacks and in patients with a family history of glucose intolerance. PTDM often reflects the substantial steroid-related weight gain that sometimes occurs after transplantation. The severity of PTDM can be attenuated by weight loss and corticosteroid withdrawal, although the latter may not be advisable owing to the risk of rejection. In a multicenter trial, PTDM occurred with greater frequency among patients treated with tacrolimus, particularly blacks. Although PTDM resolved over time in almost half of affected patients (as doses of tacrolimus and corticosteroids were gradually reduced), PTDM remained more common in patients receiving tacrolimus [25,42,43]. CyA—cyclosporine. (*From* Fujisawa USA [26]; with permission.)

Acknowledgments

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