

Care of the Renal Transplant Recipient in the Emergency Department

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End-stage renal disease is becoming more common in the United States because of the aging of the population and the increased prevalence of predisposing conditions such as diabetes and hypertension. Renal transplantation is the preferred treatment for patients with end-stage renal disease. This article reviews the medical problems that might bring renal transplant recipients to the emergency department, the information emergency physicians should be aware of in evaluating and treating these patients, and the critical importance of close communication between emergency and transplant physicians in treating them.

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INTRODUCTION

It is now established that renal transplantation is the best therapy for end-stage renal disease.¹⁻³ Renal transplantation offers a better quality of life and confers greater longevity than long-term dialysis. The susceptibility of renal transplant recipients to a variety of urgent and serious medical problems is well known to emergency physicians. Renal transplantation in the elderly is becoming more common, and transplant programs are increasingly accepting patients with significant comorbidities for transplantation.^{4,5} Diabetic nephropathy accounts for approximately 40% of the diseases leading to renal transplantation.⁶ Diabetic patients are significantly more prone to complications after renal transplantation. Because of organ shortage, the waiting period for cadaveric transplantation is increasing, which adds to the dialysis-related comorbidities in patients at transplantation.⁷ The currently available immunosuppressive drugs are more potent than those available in the past. Although this availability has resulted in a lower incidence of rejection, it has contributed to a greater incidence of medication-related problems.⁸ These factors are likely to increase the utilization of emergency medical services by renal transplant recipients.

Medical care of renal transplant recipients in the emergency department (ED) poses a number of challenges. The spectrum of medical complications in this population is different from that in the general population. Also, the classical presentation of common medical disorders may be modified by immunosuppressive medications. Adverse effects of the immunosuppressants may cause unusual problems that may not be recognized as medication related. The commonly used antirejection medications have a number of drug interactions that, if not recognized, may lead to serious complications. It is essential that emergency physicians have a good understanding of the special factors involved in treating renal transplant recipients. In this review, we present a discussion of these factors and

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highlight the complexity of caring for these patients, which necessitates close communication between emergency and transplant physicians.

SURGICAL ANATOMY OF KIDNEY TRANSPLANTATION

The transplanted kidney is placed in the right or left lower quadrant of the abdomen. Except in obese persons, the transplant is easily palpable on abdominal examination. The transplant renal artery is anastomosed to the ipsilateral internal or external iliac artery, the renal vein to the internal or external iliac vein, and the transplant ureter to the bladder.⁹ Generally, a single kidney is transplanted. When small, pediatric, or older cadaveric donor kidneys with age-related loss of renal function are transplanted, both kidneys from a donor might be placed in a single recipient to provide adequate functional renal mass.

Unlike living donor transplants that function immediately after transplant, approximately 30% of cadaveric transplants have delayed graft function because of more prolonged ischemic cold preservation.¹⁰ Continued dialytic support is required until delayed graft function resolves.

IMMUNOSUPPRESSIVE MEDICATIONS

Renal transplant recipients require lifelong immunosuppression to prevent rejection. Before 1983, immunosuppression consisted of a combination of

azathioprine and corticosteroids. The cyclosporine era began in November 1983. The most popular cyclosporine-based regimen is “triple” therapy with cyclosporine, azathioprine, and corticosteroids.⁸ Since the mid-1990s, the number of available immunosuppressants has increased. Current “triple” regimens include cyclosporine-microemulsion or tacrolimus, mycophenolate mofetil or azathioprine, and corticosteroids.¹¹ Sirolimus became available in 1999, and its incorporation into immunosuppression protocols is evolving.¹²

Immunosuppressant minimization protocols are becoming increasingly popular. These protocols involve “triple” therapy for 3 to 12 months after transplant, followed by withdrawal of 1 of the 3 drugs to minimize long-term adverse effects.¹³ The most commonly withdrawn drug is corticosteroids. Thus, a patient presenting to the ED may be receiving a combination of 2 drugs only. Comments in the rest of this article about the effects of corticosteroids apply only to patients indefinitely receiving this drug. Table 1 shows the doses and target blood levels of currently available immunosuppressants. Drug adverse effects are presented in Table 2.

In addition to the above maintenance agents, antilymphocyte antibodies are widely used in renal transplant recipients.^{14,15} Information on these antibodies is presented in Table 3. Initial therapy of rejection involves the administration of intravenous corticosteroids (methylprednisolone 250 to 1,000 mg daily for 3 days or dexamethasone 100 mg daily for 3 days).¹⁶ Sudden death, probably because of serious cardiac arrhythmias, has been

Table 1.
Currently approved maintenance immunosuppressive medications.

Medication	Typical Dose Initial/Maintenance	Target Blood Level (Trough)
Cyclosporine (Sandimmune or generic)	5–6 mg/kg PO Q12; maintenance dose determined by blood level	250–400 ng/mL (initial) 125–200 ng/mL (long term)
Cyclosporine microemulsion (Neoral or generic)	4–5 mg/kg PO Q12; maintenance dose determined by blood level	250–400 ng/mL (initial) 125–200 ng/mL (long term)
Tacrolimus (Prograf)	0.1 mg/kg PO Q12; maintenance dose determined by blood level	10–20 ng/mL (initial) 5–10 ng/mL (long term)
Azathioprine (Imuran or generic)	1.5–2.5 mg/kg PO QD (adjusted for blood counts)	Blood level monitoring not used in clinical practice
Mycophenolate mofetil (CellCept)	1.0–1.5 g PO Q12 (adjusted according to gastrointestinal adverse effects and blood counts)	Blood level monitoring not used in clinical practice
Prednisone, prednisolone, methylprednisolone	0.5 mg/kg/day (initial) 0.1 mg/kg/day (long term)	Blood level monitoring not used in clinical practice
Sirolimus (Rapamune)	2–5 mg PO QD (adjusted according to level)	10–20 ng/mL (initial) 5–15 ng/mL (long term)

PO, By mouth; Q12, every 12 h; QD, once daily.

reported when corticosteroids are given as rapid intravenous boluses.¹⁷ Intravenous infusion of corticosteroids over a 60- to 120-minute period is recommended.

A number of serious drug interactions can occur in the setting of immunosuppressive therapy.¹⁸⁻²¹ The mechanisms and possible adverse effects of these interactions are shown in Table 4. These interactions have to be considered before new medications are prescribed to renal transplant recipients.

RENAL AND URINARY TRACT PROBLEMS IN RENAL TRANSPLANT RECIPIENTS

Any disorder that can affect the native kidneys and urinary tract can also occur in the transplant recipient (eg, acute renal failure, chronic renal failure, acute on chronic renal failure, proteinuria/nephrotic syndrome,

microscopic or gross hematuria, urinary tract infections, obstructive uropathy). The only unique cause of renal failure in renal transplant recipients is rejection. Acute renal failure because of tubulointerstitial nephritis caused by the BK-polyoma virus (incidence 3% to 5%) occurs almost exclusively in renal allografts²² but has been reported in the native kidneys of AIDS patients.

The evaluation of acute renal failure in renal transplant recipients should follow the same approach as in native kidneys and exclude correctable prerenal and postrenal factors.²³ The differentiation of 2 common causes of acute renal failure after kidney transplantation, acute cyclosporine or tacrolimus nephrotoxicity and acute rejection, can be difficult without allograft biopsy. The only invariable finding in these 2 disorders is acute increase in serum creatinine level. The presence of fever and allograft tenderness favors rejection, but these findings are rare with current immunosuppressive regimens. The use of newer immunosuppressants has decreased the incidence of rejection during the first posttransplant year from 40% to 50% in the past to 15% to 25%. Elevated cyclosporine or tacrolimus blood levels make nephrotoxicity the more likely diagnosis. The blood sample for the drug level should be drawn within the 1 to 3 hours preceding the dose of the drug (trough level). Because renal transplant recipients may arrive in the ED after having taken their dose of immunosuppressants, levels obtained in this setting may not be trough levels. Low urinary fractional excretion of sodium in renal transplant recipients is not necessarily diagnostic of prerenal azotemia. Acute cyclosporine or tacrolimus nephrotoxicity and rejection may cause low fractional excretion of sodium.²⁴

Ultrasonography of the allograft is important in assessing the cause of acute renal failure.^{25,26} The demonstration of hydronephrosis implies obstructive uropathy and warrants urgent percutaneous nephrostomy. Ultrasonography also helps to identify peritransplant fluid collections. Doppler ultrasonography can help to rule out vascular causes of acute renal failure (transplant renal arterial or venous occlusion) that require prompt surgical exploration to salvage the transplant.^{27,28}

Chronic allograft nephropathy (chronic rejection) is characterized by progressive chronic renal failure and increasing proteinuria.²⁹ Approximately 40% to 50% of allograft loss after the first posttransplant year is caused by this entity. Recurrence of the native renal disease (incidence 5% to 12%) or the development of de novo renal disease in the kidney transplant is a less common cause.³⁰

Gross or microscopic hematuria could originate in the native kidneys or the allograft. Thus, imaging studies to

Table 2.

Adverse effects of maintenance immunosuppressive medications.

Medication	Adverse Effects
Cyclosporine	Acute (functional) and chronic (structural) nephrotoxicity, hyperkalemia, hypomagnesemia, hyperuricemia/gout, hemolytic-uremic syndrome, hypertension, hyperlipidemia, diabetogenicity, hepatotoxicity, neurotoxicity, hirsutism, gingival hyperplasia
Tacrolimus	Similar to cyclosporine except neurotoxicity (tremors, paresthesias, headache, insomnia, seizures) more common; hair loss (instead of hirsutism), no gingival hyperplasia; more diabetogenic; less hypertension and hyperlipidemia
Azathioprine	Bone marrow suppression, macrocytosis with or without anemia, hepatotoxicity, pancreatitis
Mycophenolate mofetil	Abdominal pain, anorexia, nausea, vomiting, upper gastrointestinal bleeding, diarrhea, anemia, leukopenia, thrombocytopenia
Corticosteroids	Weight gain, Cushingoid appearance, cataracts, acne, thinning of skin, easy bruising, osteoporosis, fractures, avascular necrosis (hip/knee), upper gastrointestinal ulceration/bleeding, diabetogenicity, psychologic effects, hyperlipidemia
Sirolimus	Thrombocytopenia, less commonly leukopenia/anemia; hyperlipidemia; buccal ulceration; diarrhea; interstitial pneumonitis

evaluate hematuria in renal transplant recipients should include the native and transplant kidneys and cystoscopy to evaluate the bladder.

Urinary tract infection in renal transplant recipients (current incidence <10% in the first posttransplant year) may involve the native kidneys or the allograft, as well as the lower urinary tract. The presence of leukocytes in the urinary sediment of renal transplant recipients does not always imply infection and may be seen during rejection. The microbiologic spectrum of urinary tract infections in renal transplant recipients is similar to that in the general population. In immunosuppressed renal transplant recipients, pyelonephritis is often severe and may result in acute renal failure. A combination of at least 2 antibiotics should be used to treat pyelonephritis in renal transplant recipients because of its severity.^{31,32} Nephrotoxic agents such as aminoglycosides are best avoided in treating urinary infection in renal transplant recipients.

SURGICAL COMPLICATIONS AFFECTING THE ALLOGRAFT

In addition to the generic postoperative complications such as atelectasis, pneumonia, wound infection, ileus,

bleeding, and venous thromboembolism, unique surgical complications affecting the allograft may occur. These include:

1. Acute occlusion of the transplant renal artery or vein: Acute occlusion usually occurs within the first posttransplant week (incidence 0.5% to 8%) and causes oligoanuria and acute renal failure. Doppler ultrasonography or radioisotopic scanning to demonstrate lack of blood flow, followed by prompt surgical exploration, may result in salvage of the allograft in a small fraction of patients with this complication. Transplant renal artery stenosis may cause hypertension or chronic renal failure.³³⁻³⁵

2. Peritransplant hematoma: This complication (incidence 2% to 3%) may occur as an early postoperative complication or in the setting of perioperative anticoagulation. Rarely, severe acute rejection may cause swelling and rupture of the transplanted kidney.³⁶ Severe pain over the allograft, with a decrease in the hemoglobin or hematocrit level and increasing serum creatinine level, is the usual presentation of this complication. Computed tomography (CT) is the best diagnostic test.³⁷ Immediate surgical exploration is required and usually leads to allograft nephrectomy. Occasionally, surgical repair of the ruptured kidney and aggressive antirejection therapy may

Table 3.

Currently approved antilymphocyte antibodies.

Medication	Indications for Use	Adverse Effects
Polyclonal antibodies Equine antithymocyte gamma-globulin (ATGAM) or rabbit antilymphocyte globulin (Thymoglobulin)	<ul style="list-style-type: none"> ● Prophylaxis against rejection in the early posttransplant period ● To provide adequate immunosuppression when nephrotoxic immunosuppressive agent (cyclosporine or tacrolimus) is withheld during delayed graft function ● Treatment of rejection unresponsive to corticosteroids 	Fever, serum sickness, anaphylaxis, leukopenia, anemia, thrombocytopenia
Monoclonal antibodies OKT ₃ (anti-CD3 antibody)	<ul style="list-style-type: none"> ● Prophylaxis against rejection in the early posttransplant period ● To provide immunosuppression when nephrotoxic agent (cyclosporine or tacrolimus) is withheld during delayed graft function ● Treatment of rejection unresponsive to corticosteroids 	During first 1–3 days of therapy: headache, aseptic meningitis, encephalopathy, seizures, nausea, vomiting, diarrhea, noncardiogenic pulmonary edema, worsening renal function. Adverse effects rare after first 3 days of therapy.
Basiliximab: IL2-receptor antibody	Same as above, but not effective in the treatment of established rejection.	Except for rare instances of anaphylaxis, no other adverse effects.
Daclizumab: IL2-receptor antibody	Same as above, but not effective in the treatment of established rejection.	Except for rare instances of anaphylaxis, no other adverse effects.

salvage the kidney. Peritransplant hematoma might cause recurrent hyperkalemia because of the release of potassium from lysis of erythrocytes in the hematoma.³⁸

3. Urinary leak: This complication usually occurs within the first posttransplant month, with an incidence of 2% to 5%. Disruption of the ureteric anastomosis to the bladder leads to extravasation of urine and acute renal failure. Obstruction of the Foley catheter perioperatively or urinary retention after removal of the catheter predisposes to urinary leak. Urinary leak is best diagnosed by the demonstration of a peritransplant fluid collection on sonography. Markedly higher concentration of urea nitrogen or creatinine levels in the percutaneous aspirate of this fluid compared with a simultaneous blood sample indicates the presence of urine and excludes lymphocele or hematoma or seroma, in which the concentrations of urea nitrogen and creatinine are close to that in the blood. Urinary leak can also be detected by radioisotopic scanning demonstrating a persistent area of radioactivity caused by the extravasation of isotope-containing urine. Institution of Foley catheter drainage, followed by prompt surgical intervention, is required to treat urinary leak.^{33,39}

4. Lymphocele: Lymph leaking from lymphatics severed during the transplant operation may result in a peritransplant fluid collection in 5% to 15% of patients,

usually within the first 3 posttransplant months. If small, a lymphocele may be asymptomatic and detected incidentally during ultrasonography. Larger lymphoceles may cause pain over the allograft, acute renal failure by extrinsic pressure on the ureter, urinary frequency by pressure on the bladder, or ipsilateral lower-extremity edema and occasionally iliac vein thrombosis or pulmonary embolism by pressure over the iliac veins. Ultrasonography is the best test to detect lymphoceles.

Symptomatic lymphoceles require percutaneous drainage into an external collection bag, followed by internal drainage into the peritoneal cavity if drainage persists.^{32,40}

5. Obstructive uropathy: The incidence of renal failure caused by obstruction is approximately 3% to 6%. In the early posttransplant period, technical problems with the ureteric anastomosis to the bladder or extrinsic compression of the ureter by a lymphocele are the common causes of obstructive uropathy. Stenosis of the transplanted ureter as a result of ischemia or previous rejection may cause obstruction months or years after transplant. The best diagnostic test is the documentation of hydronephrosis by ultrasonography. Treatment of ureteric obstruction caused by a lymphocele is discussed above. Cystoscopic retrograde stenting of the transplant ureter is technically difficult. Thus, hydronephrosis without ex-

Table 4.

Drug interactions with immunosuppressive medications.

Immunosuppressive Drug	Interacting Drug	Mechanism of Interaction	Possible Adverse Effect
Drugs metabolized by hepatic cytochrome P-450 enzyme system			
Cyclosporine or tacrolimus or sirolimus	Diltiazem, verapamil, amiodarone, keto-, flu-, or itraconazole, erythromycin, azithromycin, clarithromycin	Inhibition of cytochrome P-450 enzyme system with increased blood level of immunosuppressive drug	Nephrotoxicity caused by increased blood level of cyclosporine, tacrolimus; possible aggravation of other adverse effects of these drugs
Cyclosporine or tacrolimus or sirolimus	Phenobarbital, phenytoin, Carbamazepine, rifampin, isoniazid	Induction of hepatic cytochrome P-450 enzyme system with decreased blood level	Increased risk of rejection because of lower blood level of immunosuppressive drug
Cyclosporine or tacrolimus	HMG CoA reductase inhibitors ("statins")	Statin level increased by immunosuppressive drug	Increased risk of statin-induced rhabdomyolysis
Cyclosporine or tacrolimus	Aminoglycosides, iodinated radio-contrast, amphotericin-B	Combined nephrotoxicity of the immunosuppressive drug and the coadministered drug	Synergistic nephrotoxicity
Azathioprine	Allopurinol	Inhibition of xanthine oxidase by allopurinol decreases uric acid synthesis. Xanthine oxidase inhibition also decreases the metabolism of azathioprine, with resultant increase in azathioprine levels.	Increased azathioprine level causes bone marrow suppression

trinsic compression of the ureter requires percutaneous nephrostomy of the allograft with external drainage of urine, followed by antegrade stenting through the nephrostomy tube. Elective surgical correction of the obstruction is usually required.^{41,42}

6. Bleeding after renal allograft biopsy (incidence 1% to 3%): After allograft biopsy, patients are usually sent home after a few hours of observation. Such patients may return to the ED with gross hematuria. Resultant blood clots may cause blockage of the ureter or the bladder outlet. Severe hematuria may require blood transfusions and angiographic occlusion of the bleeding vessel.

FEVER IN RENAL TRANSPLANT RECIPIENTS

Fever is a common problem that brings renal transplant recipients to the ED. The causes of fever in these patients vary according to the time after transplant. Although the diagnostic approach to fever is similar to that in nontransplant patients, there are special considerations in assessing the febrile transplant recipient. Opportunistic infections occur frequently in these patients.⁴³⁻⁴⁵ Also, the course of an infection can be fulminant in immunosuppressed patients. Although infectious causes have to be sought aggressively, fever in renal transplant recipients may be noninfectious in origin. The reported incidence of infection of any type during the first posttransplant year is between 25% and 80%.

Infections in the First Posttransplant Month

Opportunistic infections are uncommon in the first posttransplant month. Infections seen during this period are the usual postoperative infections seen in the general surgical population, including pneumonia after general anesthesia, surgical wound infection (current incidence <1% because of routine perioperative antibiotic prophylaxis), line-sepsis, and urinary infection as a result of perioperative Foley catheterization.

Infections in the Remainder of the First Posttransplant Year

Opportunistic infections have their highest incidence after the first month and become uncommon after 6 to 12 months after transplant. A wide variety of bacterial, mycobacterial, fungal, viral, and parasitic pathogens can cause opportunistic infections in the first year.⁴³⁻⁴⁵ The respiratory tract is a common site of such infections, but the upper and lower gastrointestinal tract, the hepatobiliary system, the central nervous system, and the skin can be affected. The opportunistic infections affecting

kidney transplant patients vary geographically. Even in the same hospital, the pattern of opportunistic infections can be different in recipients of different organ transplants and may change over time in recipients of the same organ. Thus, emergency physicians should familiarize themselves with the common opportunistic infections prevalent in renal transplant recipients in their institution so that the evaluation and initial empiric antimicrobial therapy can be appropriately focused.

An opportunistic infection that is common in recipients of all types of transplants, with no significant variation in geographic prevalence, is cytomegalovirus disease, which occurs in 10% to 25% of kidney transplant recipients.^{46,47} The highest incidence of this infection is between the end of the first posttransplant month and 3 to 6 months after transplant. It can also occur after the use of potent antilymphocyte antibodies for the treatment of rejection at any time after transplant. Cytomegalovirus infection may present as cytomegalovirus disease (high fever, elevated liver function tests, and leukopenia/anemia/thrombocytopenia) or, in more severely affected persons, as tissue-invasive cytomegalovirus infection (pulmonary, upper or lower gastrointestinal, central nervous system). Cytomegalovirus infection also predisposes to superinfection with other pathogens and may be associated with acute rejection. The most reliable test to diagnose cytomegalovirus infection expeditiously is the polymerase chain reaction test for the viral DNA in the blood.

Noninfectious causes of fever in renal transplant recipients include pulmonary atelectasis in the early postoperative period, severe acute rejection, administration of antilymphocyte antibodies, and posttransplant lymphoma. Epstein-Barr virus infection underlies most cases of posttransplant lymphoma.⁴⁸

The initial evaluation of the febrile renal transplant recipient should include a CBC count with differential, serum creatinine, urinalysis, urine and blood cultures, and chest radiograph. Additional tests such as liver function tests, cytomegalovirus–polymerase chain reaction, and lumbar puncture will be required in the appropriate clinical setting. The febrile renal transplant recipient presenting in the first posttransplant year will usually require hospitalization because of the frequency of opportunistic infections and rejection during this period.

Infections After the First Posttransplant Year

Beyond the first year, although opportunistic infection may still occur, community-acquired infections unrelated to immunosuppression become more common, and, if

they are not severe, it may be possible to treat the patient without hospitalization after discussion with the transplant team.

CARDIOVASCULAR DISORDERS IN RENAL TRANSPLANT RECIPIENTS

Atherosclerotic vascular disease has a high prevalence (~15%) in renal transplant recipients and accounts for 30% to 50% of deaths after the first posttransplant year.^{49,50} The risk of cardiovascular disease is increased threefold to fivefold in kidney transplant recipients compared with that of the general population. The diagnostic and therapeutic approach to renal transplant recipients presenting with cardiac problems is not different from that in the general population. However, 2 important points are worth stressing. Given the high prevalence of ischemic heart disease in renal transplant recipients, a high index of suspicion should be maintained, however atypical the presentation might be. The other point concerns the interaction between 3 commonly used antiarrhythmic drugs (diltiazem, verapamil, and amiodarone) and 3 commonly used immunosuppressive agents (cyclosporine, tacrolimus, and sirolimus). These antiarrhythmic drugs inhibit the hepatic cytochrome P-450 enzyme system, thus elevating the level of these 3 immunosuppressive drugs, potentially leading to cyclosporine or tacrolimus nephrotoxicity. If continued therapy with diltiazem, verapamil, or amiodarone is planned, the patient should be instructed on the implications of this interaction, and the dose of the immunosuppressive drug should be adjusted downward for the duration of combined therapy.¹⁸⁻²⁰

In addition to coronary, carotid, and cerebrovascular problems, peripheral arterial occlusive disease might worsen after transplant, especially in diabetic patients, and result in ischemic ulceration and gangrene of the extremities.

HYPERTENSIVE URGENCIES AND EMERGENCIES IN RENAL TRANSPLANT RECIPIENTS

The prevalence of hypertension is high in renal transplant recipients (75% to 90% of patients).⁵¹ Hypertensive urgencies and emergencies might bring these patients to the ED. None of the parenteral or oral antihypertensive agents commonly used to treat severely elevated blood pressure is contraindicated in renal transplant recipients. However, the interaction between diltiazem or verapamil and cyclosporine, tacrolimus, or sirolimus should be

kept in mind. The patient should understand that diltiazem or verapamil should be regarded not only as an antihypertensive but also as a part of the antirejection regimen because of the effect of these drugs on the blood level of immunosuppressants.¹⁸⁻²⁰ The patient should be instructed that diltiazem or verapamil should not be discontinued or their dose changed without the knowledge of the transplant team.

PULMONARY PROBLEMS IN RENAL TRANSPLANT RECIPIENTS

The most common pulmonary problem likely to be encountered in renal transplant recipients in the ED is pneumonia. Nonopportunistic postoperative pneumonia occurs in the first month, beyond which opportunistic pulmonary infection becomes the major problem. After the first year, the community-acquired respiratory infections seen in the general population also become common in renal transplant recipients.

A wide variety of microbes can cause pneumonia in renal transplant recipients. The pattern of the pulmonary infiltrate on the chest radiograph can give important clues about the nature of pulmonary infection. Lobar consolidation is suggestive of Legionella, pneumococcal, or other bacterial pneumonia, nodular or cavitating lesions indicate fungal infections, and a bilateral interstitial pattern suggests *Pneumocystis carinii* or cytomegalovirus pneumonia.⁵²⁻⁵⁴ Interstitial pneumonitis has also been associated with sirolimus therapy.⁵⁵ In transplant recipients, chest radiograph might not be conclusive in the early stages of respiratory infection, and CT scanning might be required to identify pulmonary infiltrates. Noncardiogenic pulmonary edema as a result of increased capillary permeability may occur after the initial 2 or 3 doses of OKT₃ (Muromonab-CD3), especially in already fluid-overloaded individuals.¹⁵

The threshold for hospitalization for suspected pneumonia in immunosuppressed renal transplant recipients should be lower than in the general population because it can have a fulminant course. If erythromycin, azithromycin, or clarithromycin is chosen for therapy of pneumonia, the dose of cyclosporine, tacrolimus, and sirolimus should be reduced for the duration of therapy with these antibiotics because they inhibit the hepatic enzyme system that metabolizes the immunosuppressants mentioned above.¹⁸⁻²⁰ Every attempt should be made to obtain good sputum samples for microbiologic studies before institution of empiric antibiotic therapy, given the unusual

spectrum of organisms causing pneumonia in renal transplant recipients.

GASTROINTESTINAL PROBLEMS IN RENAL TRANSPLANT RECIPIENTS

Disorders of the gastrointestinal tract are common after renal transplantation, occurring in 3% to 30% of recipients, and may affect any part from the oral cavity to the large bowel.⁵⁶⁻⁵⁸ The gastrointestinal problems encountered in renal transplant recipients are shown in Table 5. The severity of acute abdominal conditions such as upper gastrointestinal perforation or colonic diverticular rupture may be blunted by immunosuppressants, especially corticosteroids. Even apparently mild pain should prompt imaging studies such as an acute abdominal series or CT scanning in renal transplant recipients.

HEPATOBIILIARY AND PANCREATIC DISORDERS IN RENAL TRANSPLANT RECIPIENTS

Abnormalities in liver function tests occur frequently in renal transplant recipients. The common causes of hepatic dysfunction in renal transplant recipients are presented in Table 5.⁵⁸⁻⁶⁰ The clinical presentation of acute cholecystitis may be blunted by immunosuppressive therapy, especially corticosteroids.⁶¹ The incidence and severity of acute pancreatitis appear to be increased in renal transplant recipients.^{62,63} In addition to cholelithiasis and alcohol, pancreatitis in renal transplant recipients may be caused by other disorders shown in Table 5.

NEUROLOGIC AND PSYCHOLOGIC DISORDERS IN RENAL TRANSPLANT RECIPIENTS

Neurologic complications in renal transplant recipients could result from adverse effects of immunosuppressive drugs, opportunistic infection, or malignancy. Tacrolimus and cyclosporine can cause similar neurologic adverse effects (eg, headache, insomnia, tremors, paresthesias, cramps affecting the extremities), but the incidence is much higher with the former drug.⁶⁴ Less commonly, seizures and global encephalopathy have been associated with these 2 drugs. The neurologic adverse effects are dose and blood level related. The initial doses of OKT₃ may cause severe headache, aseptic meningitis, and global encephalopathy.⁶⁵

Opportunistic central nervous system infections occur in 5% to 10% of renal transplant recipients. *Listeria monocytogenes*, *Cryptococcus*, and *Mycobacterium tuberculosis* are the pathogens most likely to cause meningeal infection in this population.⁶⁶⁻⁶⁸ Encephalitis or meningoencephalitis could result from cytomegalovirus, toxoplasma, or herpes simplex infection. West Nile encephalitis has been reported in renal transplant recipients.⁶⁹

Posttransplant lymphoma commonly involves the central nervous system and, depending on its site and extent, may cause headache and a variety of neurologic deficits.⁴⁸ Headache in the immunosuppressed renal transplant recipient should be considered potentially serious and warrants lumbar puncture and prompt imaging studies of the brain. Depression and suicide are more prevalent in renal transplant recipients.^{70,71} Steroid psychosis might underlie psychologic problems in this population.

HEMATOLOGIC DISORDERS IN RENAL TRANSPLANT RECIPIENTS

Anemia, leukopenia, thrombocytopenia, or combinations of these hematologic abnormalities are common in renal

Table 5. Gastrointestinal, hepatobiliary, and pancreatic problems in renal transplant recipients.

Problem	Causes
Buccal/labial ulceration	Candida/herpes simplex; sirolimus
Esophagitis/dysphagia	Candida/herpes simplex/CMV; mycophenolate mofetil
Gastroduodentis, upper gastrointestinal ulceration and bleeding, anorexia, nausea, vomiting	CMV infection; mycophenolate mofetil, corticosteroids; intestinal lymphoma
Diarrhea, colonic ulceration, lower gastrointestinal bleeding	CMV infection; mycophenolate mofetil; sirolimus; intestinal lymphoma
Acute hepatic dysfunction (increased liver enzymes, bilirubin)	CMV, Epstein-Barr virus; cyclosporine, tacrolimus, azathioprine
Chronic hepatic dysfunction	Hepatitis C more commonly than hepatitis B; azathioprine
Pancreatitis	CMV infection; hypercalcemia/hypertriglyceridemia; azathioprine, possibly related to corticosteroids

CMV, Cytomegalovirus.

transplant recipients. Azathioprine, mycophenolate mofetil, and sirolimus may cause these changes.⁷² Sulfatrimethoprim, given for *Pneumocystis carinii* pneumonia prophylaxis, and ganciclovir or valganciclovir, given for cytomegalovirus prophylaxis, cytomegalovirus, and other viral infections, can be associated with cytopenias.⁴⁶ Administration of equine antithymocyte gamma-globulin (ATGAM) or Thymoglobulin can lower blood cell counts due to antileukocyte, anti-erythrocyte, and antiplatelet antibodies contaminating these polyclonal antilymphocyte antibodies. The prevalence of anemia is 21% at 1 year and 36% at 3 years after transplant.⁷³ The 3 immunosuppressants mentioned above and chronic renal failure as a result of chronic rejection are the major causes of posttransplant anemia. The combination of anemia, thrombocytopenia, and acute renal failure should suggest the possibility of hemolytic-uremic syndrome. Hemolytic-uremic syndrome in renal transplant recipients has been associated with cyclosporine or tacrolimus therapy, acute vascular rejection, and cytomegalovirus infection.⁷⁴⁻⁷⁶ Elevated lactate dehydrogenase, low haptoglobin levels, and the presence of schistocytes in the peripheral blood smear are diagnostic clues to hemolytic-uremic syndrome. Parvovirus B19 infection has been associated with the development of pure RBC aplasia and anemia in renal transplant recipients.⁷⁷

Corticosteroids used for immunosuppression can cause leukocytosis because of demargination of leukocytes adherent to vascular endothelium.⁷⁸ Band forms are characteristically absent in corticosteroid-associated leukocytosis, and their presence should lead to a search for infection. Complete corticosteroid withdrawal can lead to leukopenia.

Posttransplant erythrocytosis occurs in approximately 10% to 20% of renal transplant recipients during the first posttransplant year and persists long term in approximately half the affected individuals.^{79,80} Posttransplant erythrocytosis may cause nonspecific symptoms such as dizziness and headaches and predispose to thromboembolic complications. Venesection may be required as initial treatment for posttransplant erythrocytosis, and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker therapy can decrease erythropoiesis and prevent recurrence of posttransplant erythrocytosis.^{79,81}

Parasitic infections should be considered when eosinophilia is discovered in renal transplant recipients. Strongyloidosis is a rare but serious problem in renal transplant recipients because the parasitic larvae can transport other microbes to different parts of the body and result in fulminant sepsis.⁸²

MUSCULOSKELETAL AND ARTICULAR COMPLICATIONS IN RENAL TRANSPLANT RECIPIENTS

Corticosteroids and, to a lesser extent, cyclosporine and tacrolimus cause osteoporosis, and bone loss averages 1% to 2% per year after transplant.⁸³ For unclear reasons, the most common site of the resultant fractures is the bones of the feet. Hip, wrist, and vertebral fractures are less common. Unexplained pain in the feet in renal transplant recipients may be the result of stress fractures that might be subtle enough to be missed on plain radiographs and may require isotopic bone scan or magnetic resonance imaging (MRI) for diagnosis.⁸³⁻⁸⁵

Hyperuricemia and gout are common in cyclosporine- and tacrolimus-treated patients because of decreased renal excretion of uric acid. Gout must be included in the differential diagnosis in evaluating articular symptoms in renal transplant recipients.⁸⁶ Caution is required when nonsteroidal anti-inflammatory drugs (including selective Cox-2 inhibitors) and colchicine are used to treat gout in renal transplant recipients. The former can worsen renal function, and the latter may interact with cyclosporine and result in acute elevation of liver function tests, leukopenia, proximal muscle weakness, and rhabdomyolysis.⁸⁷ When allopurinol is used to decrease the uric acid level in azathioprine-treated patients, severe bone marrow suppression can occur unless the azathioprine dose is reduced.¹⁸⁻²⁰

Avascular necrosis (incidence of 1% to 30% in different reports) of the hip and, less commonly, the knee can be the cause of pain in these joints in renal transplant recipients. MRI is more sensitive than plain radiographs in detecting avascular necrosis in its early stages.⁸⁸

When corticosteroids are withdrawn completely, some renal transplant recipients develop generalized myalgias and arthralgias that respond to reinstitution of very small doses of prednisone (2.5 to 5 mg/day).^{78,89}

Tendon rupture affecting the Achilles or quadriceps tendon may occur in renal transplant recipients, even with minimal trauma. Chronic corticosteroid therapy and tendon calcification resulting from secondary hyperparathyroidism are the major causative factors.⁹⁰ The use of quinolone antibiotics has been associated with tendon rupture in renal transplant recipients.⁹¹ This complication should be suspected in patients presenting with pain over the Achilles or quadriceps tendon. The best test to diagnose tendon rupture is soft tissue ultrasonography.

Sudden, severe attacks of bone pain in the vicinity of the joints in the lower extremity, attributed to bone

infarction or marrow swelling, have been reported in cyclosporine- or tacrolimus-treated patients.⁹² Calcium channel blockers such as nifedipine have relieved the pain in some patients.

CUTANEOUS PROBLEMS IN RENAL TRANSPLANT RECIPIENTS

A variety of dermatologic problems can occur after renal transplantation,⁹³⁻⁹⁷ including acne as a result of corticosteroids, herpes zoster, human papilloma virus-related viral warts, skin malignancies (squamous cell carcinoma more commonly than basal cell carcinoma), human herpes virus 8-related Kaposi's sarcoma, and perianal or vulvar condylomata and carcinomas (related to human papilloma virus infection). Skin nodules and ulcers in renal transplant recipients may be the result of opportunistic mycobacterial or fungal infections. Skin biopsy with appropriate histologic and microbiologic studies is indicated in the evaluation of these lesions.^{93,97}

COMMON ELECTROLYTE ABNORMALITIES IN RENAL TRANSPLANT RECIPIENTS

Cyclosporine and tacrolimus decrease potassium excretion and increase magnesium excretion in the urine, with resultant hyperkalemia and hypomagnesemia.⁹⁸ Sulfa-trimethoprim, angiotensin-converting enzyme inhibitor, or angiotensin II receptor blocker therapy can also contribute to hyperkalemia.⁹⁹

Persistence of secondary hyperparathyroidism of renal failure posttransplant (incidence 5% to 10%) in the setting of a functioning transplant capable of synthesizing 1-25 dihydroxyvitamin D3 and excreting phosphate may cause hypercalcemia and hypophosphatemia.^{100,101}

Nonanion gap metabolic acidosis could be the result of tubular dysfunction resulting from acute or chronic rejection of the kidney transplant.¹⁰² Advanced renal failure of the allograft may cause high-anion gap metabolic acidosis.

NEW-ONSET POSTTRANSPLANT DIABETES MELLITUS

De novo diabetes occurs in 5% to 20% of renal transplant recipients.¹⁰³ Corticosteroids, cyclosporine, and tacrolimus contribute to this complication. Tacrolimus appears to be more diabetogenic than cyclosporine. Obesity; family history of diabetes; black, Hispanic, or Native American ethnicity; older age; and hepatitis C infection are other risk

factors for diabetes mellitus. Rapid weight loss, polyuria, thirst, and fluctuating visual acuity should suggest the diagnosis of posttransplant diabetes mellitus.

STRESS-DOSE CORTICOSTEROID COVERAGE

Severely ill renal transplant recipients presenting to the ED will require stress-dose corticosteroid coverage (hydrocortisone 50 to 100 mg intravenously every 6 to 8 hours) to avoid acute adrenal insufficiency, unless the patient has not been receiving corticosteroids for more than 6 to 12 months.¹⁰⁴

In conclusion, renal transplant recipients frequently utilize ED services because of their proneness to a variety of emergency medical problems. It is imperative that emergency physicians become aware of the special considerations in treating these patients. The complexities of medical problems, the rapidly changing medication regimens, and the high potential for drug interactions in renal transplant recipients make close communication between emergency and renal transplant physicians critical when these patients seek care in the ED.

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