Renal Transplant Complications

Gerald Maloney

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Surgical complications that may be seen in the emergency department include hematoma formation, ureteral anastomotic leak, and ureteral obstruction. Computed tomography is the diagnostic imaging modality of choice for these surgical emergencies.

Surgical infections that are common in the first posttransplant month include pneumonia, line sepsis, and wound infection. Opportunistic infections reach their peak incidence during the remainder of the first posttransplant year. After the first year, community-acquired infections predominate.

Renal transplant patients have a high risk for atherosclerotic disease. Cardiovascular conditions account for 30% to 50% of deaths during the first posttransplant year.

Fluoroquinolones and macrolides may increase levels of cyclosporine and tacrolimus; these antibiotic classes should not be used as first-line agents for the treatment of patients with posttransplant pneumonia.

Fever and tenderness over the graft site may indicate acute rejection.

Transplant recipients treated with corticosteroid therapy have functional adrenal insufficiency and require pulse doses of corticosteroids when they encounter physiologic stress.

KEY POINTS

- Renal transplantation is highly successful. With appropriate immunosuppressive therapy, the rate of acute rejection during the first posttransplant year is less than 25%; 1-year survival rates approach 100%.
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- Transplant recipients treated with corticosteroid therapy have functional adrenal insufficiency and require pulse doses of corticosteroids when they encounter physiologic stress.

EPIDEMIOLOGY

The kidney is the most commonly transplanted solid organ. According to the U.S. Organ Procurement and Transplantation Network, more than 298,260 kidney transplants have been performed to date. It is important that providers have a general understanding of the expected surgical and medical complications commonly observed in posttransplant patients.

DEVELOPMENTS IN RENAL TRANSPLANTATIONS

The primary indication for renal transplantation is stage V chronic kidney disease (formerly called end-stage renal disease). Transplantation is recognized as the most effective form of renal replacement therapy for these patients.

Specific disease entities that causing chronic kidney disease are outlined in Box 117.1. Diabetic nephropathy is the most common single disease process leading to renal transplantation.1

Most renal grafts now function for longer than 10 years. The 1-year survival rate of renal transplant recipients is 95% to 98%. Renal transplants are more effective than hemodialysis at prolonging the life of patients with chronic kidney disease.2

Previously, the highest surgical success rates were achieved with histologically matched donor kidneys from a living recipient. Advances in immunosuppressive medication regimens have improved the success rate of cadaveric kidney transplantation, which now approaches that seen with living donors.

Preoperative clearance for renal transplantation is extensive. For patients with cancer, the suggested disease-free interval before transplantation is 5 years. Infection with human immunodeficiency virus is considered a contraindication to renal transplantation in many institutions, although transplantation has been successful in many patients with well-maintained CD4+ T-cell counts.

Cholecystectomy was previously performed in all patients undergoing renal transplantation. Currently, cholecystectomy is performed only in patients with evidence of cholelithiasis or cholecystitis.

The surgical approach to renal transplantation varies with the age of the patient, as well as with the location of the kidney and the anastomosis. The recipient’s native kidneys and collecting system are generally left in place unless there is another indication for nephrectomy. The donor kidney is placed in one of the lower abdominal quadrants (more commonly the right), and the ureter is anastomosed to the bladder; arterial and venous anastomoses generally arise from the iliac vessels, aorta, or inferior vena cava. The transplanted kidney is usually palpable on abdominal examination.

Immunosuppression is initiated after transplantation and is divided into two phases: induction and maintenance.1 Agents such as tacrolimus and monoclonal and polyclonal antibodies are often included in the induction and maintenance phases of treatment (Box 117.2). With the use of immunosuppressive medications, the 1-year incidence of acute rejection is 15% to 25%.

COMPLICATIONS

Complications of renal transplantation can be categorized by cause as either surgical or medical and further divided by time of occurrence as either early or delayed.
SURGICAL COMPLICATIONS

Surgical complications include graft malfunction, thrombosis, aneurysms of the graft vessels, and stricture or obstruction of the ureter. Some of these complications will be evident shortly after surgery; others may occur years after the procedure and cause symptoms that will probably prompt emergency department (ED) evaluation.

Graft function may be delayed in up to 30% of cadaveric transplants, probably as a result of prolonged cold ischemia of the kidney during the period between harvesting and transplantation. Delayed graft function is a rare complication with living donor transplants. Patients may require continued dialysis until adequate posttransplant function is demonstrated.

Acute thrombosis of the arterial or venous anastomoses is usually seen within the first posttransplant week. Treatment is surgical exploration in an attempt to salvage the donor kidney.

Renal artery stenosis has been reported in allografts and can cause hypertension in posttransplant patients. This is generally a delayed complication. Aneurysms of the graft vessels are uncommon, delayed events.

Hematomas may develop around the transplanted kidney. Hematoma formation may be an early postoperative complication or rarely may result from acute rejection with spontaneous rupture of the kidney. Acute hematomas are surgical emergencies.

Ureteral complications include anastomotic leakage (generally within the first posttransplant month), acute ureteral obstruction, and lymphocele. These complications will occur within the first 3 months following transplantation. Computed tomography of the abdomen is the preferred imaging modality for ureteral complications. Ureteral obstruction often requires emergency surgical intervention.

MEDICAL COMPLICATIONS

Medical complications are numerous and often subtle. Posttransplant patients are at risk for atypical infections, cardiovascular death, renal failure, and rejection. Adverse reactions from immunosuppressive medications account for many delayed medical complications in transplant patients.

Fever

Management of fever in posttransplant patients should be approached similar to that of fever in other immunocompromised patients. Because of suppressed immunologic and inflammatory responses, posttransplant patients may not exhibit the common findings of acute infection. Fever may or may not be associated with clinically significant infection.

Acute rejection is one cause of fever that may develop at any time. Decisions regarding appropriate diagnostic testing and disposition of a posttransplant patient with fever should be made in consultation with a transplant service.

Infections

The incidence of infection in the first posttransplant year has been reported to be as high as 25% to 80%. Expected infections vary according to posttransplant time (Box 117.3). Infections in the first posttransplant month are typical postoperative infections—pneumonia, sepsis from central lines or urinary catheters, and wound infections. Atypical or opportunistic infections are uncommon.

After the first month through the end of the first posttransplant year, opportunistic infections reach their peak incidence. A variety of atypical bacterial, viral, fungal, protozoal, and parasitic infections may occur. Individual transplant services maintain current information on the opportunistic infections seen in their institution. Cytomegalovirus is one of the most common opportunistic infections and occurs in up to 25% of renal transplant recipients. It can cause systemic or invasive disease and is associated with acute rejection.

After the first year, the incidence of opportunistic infections decreases and typical community-acquired pathogens predominate.

Leukocytosis is a poorly sensitive and inconsistent indicator of the source of the fever, and therefore a normal white blood cell count should not be used to exclude a potential infectious illness in a transplant patient. Peritoneal findings

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**BOX 117.1 Diseases Leading to Renal Transplantation**

<table>
<thead>
<tr>
<th>Disease</th>
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<tbody>
<tr>
<td>Chronic kidney disease</td>
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<td>Polycystic kidney disease</td>
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<td>Trauma</td>
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**BOX 117.2 Common Immunosuppressive Drugs Used in Renal Transplant Recipients**

<table>
<thead>
<tr>
<th>Drug</th>
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<tbody>
<tr>
<td>Cyclosporine (Sandimmune, Neoral)</td>
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<tr>
<td>Tacrolimus (Prograf)</td>
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<tr>
<td>Azathioprine (Imuran)</td>
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<tr>
<td>Mycophenolate mofetil (CellCept)</td>
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<tr>
<td>Sirolimus (Rapamune)</td>
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<tr>
<td>Prednisone</td>
</tr>
<tr>
<td>methylprednisolone</td>
</tr>
<tr>
<td>Polyclonal antithymocyte</td>
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<tr>
<td>globulin</td>
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<tr>
<td>Rituximab</td>
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<td>Daclizumab</td>
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**BOX 117.3 Infections in Posttransplant Patients**

**First Month After Transplantation**

Typical postsurgical infections (pneumonia, urinary tract infection, line sepsis, wound infection)

Opportunistic infections uncommon

**Infections in the First Posttransplant Year**

Opportunistic infections (*Pneumocystis pneumoniae*, *Cryptococcus*, fungal infections, viral infections; highest incidence in months 2 to 6)

Cytomegalovirus (most common)

Tuberculosis

**Infections More Than 1 Year After Transplantation**

Community-acquired more common than opportunistic infections

Typical organisms causing cellulitis, pneumonia, urinary tract infections
**Renal Transplant Complications**

1. **Transplantation, and history of recent hospitalization.**

2. **likely organisms based on the clinical findings, time after transplantation, and history of recent hospitalization.**

3. **Antimicrobial choices need to be tailored to the most likely organisms based on the clinical findings, time after transplantation, and history of recent hospitalization.**

4. **Chest computed tomography may be required to help delineate the cause of abnormal findings on chest radiography.**

5. **The threshold for hospital admission of posttransplant patients with pneumonia is lower given the potential for patients with serious intraabdominal processes to have relatively minimal findings on physical examination.**

6. **Mortality from cholecystitis is high in renal posttransplant patients. Diverticulitis is the most common bacterial gastrointestinal infectious process.**

7. **Abdominal pain in the area of the allograft should prompt consideration of acute rejection.**

8. **Opportunistic infections may affect any area of the gastrointestinal tract, from the mouth to the anus. Common opportunistic infections include candidiasis, cytomegalovirus, and herpes simplex.**

9. **Cytomegalovirus and Epstein-Barr virus can cause acute hepatitis.**

10. **Various immunosuppressive drugs can cause stomatitis, ulcerations, or acute hepatitis.**

11. **Renal transplant recipients have an increased incidence of acute pancreatitis that may be related to immunosuppressive agents.**

12. **Renal transplant recipients are prone to the same genitourinary and renal disorders as the general population. The one truly unique renal emergency in this population is rejection.**

13. **Urinary tract infections are more severe in transplant recipients.**

14. **Pneumonitis has been noted to cause interstitial pneumonitis.**

15. **Chest computed tomography may be required to help delineate the cause of abnormal findings on chest radiography.**

16. **If hydronephrosis is present, ultrasound studies should be ordered to look for ureteral obstruction. Arterial Doppler imaging may be needed to evaluate the adequacy of blood flow to a graft. Obstruction of an allograft is a true surgical emergency that generally requires placement of a percutaneous nephrostomy tube.**

17. **Rejection can be acute, chronic, or acute on chronic. Acute rejection occurs in the early posttransplant period. Chronic rejection is the most common cause of renal allograft dysfunction after the first posttransplant year.**

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**Box 117.4 Drug Interactions in Patients Taking Immunosuppressive Medications**

- **Cyclosporine**
  - Levels increased (potential nephrotoxicity) by diltiazem, verapamil, azole antifungals, macrolides
  - Levels decreased (potential subtherapeutic levels and risk for rejection) by phenobarbital, phenytoin, carbamazepine, isonicotinic hydrazine (INH), rifampin, nafcillin
  - Aminoglycosides—can exacerbate nephrotoxicity
  - Statins—may predispose to hepatotoxicity or rhabdomyolysis; cyclopentolate may increase statin levels

- **Azathioprine**
  - Allopurinol—levels of azathioprine increased, which results in an increased risk for myelosuppression

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**Cardiovascular Emergencies**

Because the majority of renal transplant recipients in the United States have diabetes or hypertension (or both), the risk for concomitant cardiovascular disease is high. Furthermore, the combination of cyclosporine and corticosteroids worsens dyslipidemias and atherogenesis. Cardiovascular disease accounts for 30% to 50% of deaths in the first posttransplant year, and the incidence of atherosclerotic vascular disease is up to five times greater in transplant recipients than in other hospitalized patients.

- The approach to diagnosis and management of suspected cardiac ischemia in the posttransplant population is similar to that in the general population; however, higher-risk stratification for these patients is critical.

- Varying degrees of hypertensive urgencies or emergencies may be seen in posttransplant patients. Likewise, patients may have acute or chronic dysrhythmias (e.g., chronic atrial fibrillation) unrelated to the transplant. Although no single antihypertensive or antidyssrhythmic agent is contraindicated, care should be taken to avoid drug interactions (Box 117.4).

**Pulmonary Emergencies**

Pneumonia remains the most common pulmonary emergency in transplant recipients. The causative organisms vary depending on the timing after transplantation. Chest radiograph findings may be nonspecific; immunosuppressive medications blunt the appearance of infiltrates. Additionally, sirolimus has been noted to cause interstitial pneumonitis. Chest computed tomography may be required to help delineate the cause of abnormal findings on chest radiography.

The threshold for hospital admission of posttransplant patients with pneumonia is lower given the potential for rapidly progressive disease and opportunistic infections. Appropriate effort should be made to obtain sputum for Gram stain and culture because of the potential for unusual organisms. Antimicrobial choices need to be tailored to the most likely organisms based on the clinical findings, time after transplantation, and history of recent hospitalization.

Fluoroquinolones and macrolides may increase levels of cyclosporine and tacrolimus; these antibiotic classes should not be used as first-line agents for the treatment of patients with posttransplant pneumonia. Discussion with the transplant service may be beneficial in determining the preferred choice of antibiotic.

**Gastrointestinal Emergencies**

Abdominal pain in renal transplant recipients may be due to a variety of causes. Diagnostic imaging studies should be used liberally given the potential for patients with serious intraabdominal processes to have relatively minimal findings on physical examination.

- Mortality from cholecystitis is high in renal posttransplant patients. Diverticulitis is the most common bacterial gastrointestinal infectious process. Diarrhea may be due to any number of infectious organisms, including Salmonella, Listeria, cytomegalovirus, and Cryptosporidium.

- Abdominal pain in the area of the allograft should prompt consideration of acute rejection.

- Opportunistic infections may affect any area of the gastrointestinal tract, from the mouth to the anus. Common opportunistic infections include candidiasis, cytomegalovirus, and herpes simplex.

- Cytomegalovirus and Epstein-Barr virus can cause acute hepatitis.

- Various immunosuppressive drugs can cause stomatitis, ulcerations, or acute hepatitis.

- Renal transplant recipients have an increased incidence of acute pancreatitis that may be related to immunosuppressive agents.

**Genitourinary and Renal Emergencies**

Renal transplant recipients are prone to the same genitourinary and renal disorders as the general population. The one truly unique renal emergency in this population is rejection.

- Urinary tract infections are more severe in transplant recipients.

- Pyleonephritis may follow a fulminant course.

- Infection (cytomegalovirus), rejection, or medication toxicity can cause acute hepatitis.

- Various immunosuppressive drugs can cause stomatitis, ulcerations, or acute hepatitis.

- Renal transplant recipients have an increased incidence of acute pancreatitis that may be related to immunosuppressive agents.

**Drug Interactions in Patients Taking Immunosuppressive Medications**

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- **Azathioprine**
  - Allopurinol—levels of azathioprine increased, which results in an increased risk for myelosuppression
A common cause of acute renal failure in renal transplant patients is nephrotoxicity from cyclosporine or tacrolimus. Rejection may not be able to be distinguished from nephrotoxicity without a biopsy. Fever and tenderness over the graft site suggest the presence of rejection, whereas elevated trough levels of cyclosporine or tacrolimus suggest drug-induced nephrotoxicity.

If acute rejection is the most likely diagnosis, the transplant service should be consulted for inpatient management and high-dose methylprednisolone therapy begun at 500 to 1000 mg daily.

**Endocrine and Metabolic Emergencies**

Transplant recipients receiving corticosteroid therapy have functional adrenal insufficiency and require pulse doses of corticosteroids when they encounter physiologic stress. Stress-dose hydrocortisone should be administered to transplant patients with unexplained or refractory hypotension unless they have not been taking corticosteroids for more than 6 months.

Electrolyte disorders, especially hyperkalemia, are common in posttransplant patients as a result of cyclosporine- or tacrolimus-induced impairment of potassium excretion. This impairment may be exacerbated by the use of potassium-sparing diuretics and angiotensin-converting enzyme inhibitors.

Cyclosporine and corticosteroids both contribute to an increased incidence of new-onset diabetes in transplant recipients.

**Neurologic Emergencies**

Cryptococcal meningitis and central nervous system lymphoma are seen with greater frequency in posttransplant patients because of the immunosuppression. Patients with fever of unknown origin, headache, or altered mental status should undergo intracranial imaging and lumbar puncture as appropriate. Computed tomography scanning of the brain with and without contrast enhancement is preferable in this population to more readily identify space-occupying lesions. The risk for contrast-induced nephrotoxicity must be weighed against the benefit of diagnostic accuracy when brain lesions are suspected. Similarly, use of gadolinium-enhanced magnetic resonance imaging may be contraindicated given the risk for nephrogenic systemic fibrosis in patients with abnormal creatinine clearance.

**Adverse Drug Reactions**

Immunosuppressive medications cause illness through the direct toxic effects of these drugs or through interaction with other common medications. Medication reconciliation is critical as new drug regimens become more complex.

Initial posttransplant regimens typically consist of three agents: a corticosteroid, a calcineurin inhibitor (cyclosporine, tacrolimus, sirolimus), and a purine synthesis inhibitor (azathioprine, mycophenolate mofetil). Most patients are weaned off corticosteroids in 6 months, and maintenance is continued with only two drugs.

During the initial induction phase of immunosuppression, other agents such as antithymocyte monoclonal and polyclonal antibodies are used. Because these medications are generally reserved for inpatient use, it is unusual for patients to be seen in the ED with an acute complication from these agents.

Corticosteroid therapy has many well-recognized complications. In addition to functional adrenal suppression, corticosteroids can induce diabetes, steroid psychosis, gastric ulceration, pancreatitis, changes in body habitus, and avascular necrosis.

Azathioprine is one of the oldest agents used to treat rejection. It is an alkylating agent similar to other chemotherapeutic drugs, and thus its primary toxicity is bone marrow suppression (particularly leukopenia). When given with allopurinol, increased levels of azathioprine may result in myelosuppression. Azathioprine and mycophenolate mofetil demonstrate an additive risk for myelosuppression. The hepatotoxicity from azathioprine is less than that with other agents.

Cyclosporine interacts with multiple other medications and demonstrates significant nephrotoxicity. Increased serum creatinine levels are observed in up to one third of patients taking cyclosporine. As these levels rise, cyclosporine excretion decreases and renal failure worsens. Trough measurements of cyclosporine (3 hours before the next scheduled dose) differentiate drug-induced nephrotoxicity from other causes of renal insufficiency.

Tacrolimus and sirolimus both carry a risk for multiple drug interactions and worsening nephrotoxicity. Drugs that increase the metabolism of these agents may decrease their effective serum levels and thus result in acute rejection because of inadequate immunosuppression.

**DISPOSITION**

Concerns about chronic immunosuppression, graft rejection, and multiple drug interactions make management of transplant patients among the most difficult challenges encountered in the ED. As a rule, these patients require extensive laboratory and imaging studies; there are no data to predict which of these patients can safely forgo such testing in an emergency setting. Consultation with an experienced transplant team will improve outcomes. The majority of transplant patients with serious chief complaints require hospital admission for observation and further management.

**SUGGESTED READINGS**


**REFERENCES**

References can be found on Expert Consult @ www.expertconsult.com.
REFERENCES