The Renal Transplant Patient

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Abstract: Renal transplant recipients commonly present to the emergency department (ED) with a wide variety of medical problems. In this chapter, we present a review of the common medical conditions that bring these patients to the ED, the special considerations in their evaluation and management, adverse effects of the commonly used medications and the possibility of serious drug interactions that the emergency physician should be aware of when providing care to this population. Given the complexities of medical management of these patients, prompt and detailed communication between emergency physicians and the transplant team is imperative to provide quality care to this population in the ED.

Keywords:
Renal Transplantation
Emergency Department
Introduction and Epidemiology

End-stage renal disease (ESRD) is a major and growing global public health problem. Renal transplantation is the preferred treatment option for ESRD because it confers improved quality of life and longevity compared to dialysis. Currently in the United States, approximately 160,000 ESRD patients have their lives sustained by a functioning kidney transplant and worldwide, the number of renal transplant recipients is approximately three times this number.(1)

Renal transplant recipients are prone to a variety of serious medical problems that cause them to seek care in the emergency department (ED). Over the past two decades the risk of developing such emergent medical problems has increased significantly in the transplant population for a variety of reasons. There is an increasing acceptance of transplantation for older patients with a number of serious comorbidities such as diabetes and cardiovascular disease. There is also an increasing length of time spent on dialysis awaiting a deceased-donor transplant (up to 4 to 5 years in many patients) that adds dialysis-related co-morbidities. Finally, the availability of more potent immunosuppressive drugs has reduced the risk of acute rejection, but increased the risk of drug-related adverse effects including opportunistic infections and malignancies.(2)

The emergency physician must be aware of a number of unique considerations in evaluating and managing the renal transplant patient. These patients may present with disorders that are uncommon in the general patient population. They may also present with blunted symptoms of common disorders as a results of immunosuppressive drugs,
especially corticosteroids. The presenting complaint of renal transplant recipients may be
due to the adverse effect of drugs unique to the transplant population with which
emergency physicians may be unfamiliar. There are multiple serious drug-interactions
with immunosuppressive medications, and the possibility that the patient’s symptoms
may be the result of such an interaction must always be entertained. Care should be
exercised while prescribing new medications or altering the renal transplant patient's
current medications as this may lead to serious drug-interactions and alterations in the
blood level of immunosuppressive drugs.(2)

This chapter will present a review of background aspects of renal transplantation
pertinent to emergency physicians followed by an organ-system based discussion of the
medical problems that might result in presentation of the renal transplant recipient to the
ED.

**Surgical Aspects of Renal Transplantation**

Knowledge of the surgical anatomy of the kidney transplant (allograft) is essential for the
proper evaluation of the renal transplant patient. The allograft is usually placed extra-
peritoneally in the right or left lower abdominal quadrant. Occasionally, for technical
reasons, the transplanted organ is placed intra-peritoneally. The operation involves three
anastamoses (Figure): renal artery and vein of the allograft to the recipient’s ipsilateral
internal or external iliac artery and vein, respectively and the ureter of the allograft to the
recipient’s bladder (ureteroneocystostomy).(3)
A single kidney is transplanted into most recipients. Occasionally, because of the concern of inadequate nephron mass in a small kidney, both kidneys from a pediatric donor (placed en bloc in one or other lower abdominal quadrant) or both kidneys from an older donor with age-related loss of nephron mass (placed one on each side) are transplanted. Because of a shorter period of ischemic preservation after removal from the donor prior to transplantation, most living-donor transplants function immediately with no need for postoperative dialysis. However, up to one third of cadaveric donor transplants do not function immediately (due to the longer period of ischemic preservation), and dialysis may be required until transplant kidney function is established.
- a condition referred to as delayed graft function (DGF).(4, 5) A well functioning kidney transplant usually results in a post-transplant nadir serum creatinine (SCr) level lower than 1.5 to 2.0 mg/dL.

**Post-Transplant Immunosuppression Regimens**

With the exception of the very rare recipient of a kidney from an identical twin donor, renal transplant recipients require lifelong maintenance anti-rejection therapy. In the immediate post-transplant period with its attendant risk of acute rejection, a combination of three drugs (“triple therapy”) is used for immunosuppression: a calcineurin-inhibitor ([CNI]-cyclosporine or tacrolimus) plus an anti-lymphocyte proliferative agent (mycophenolate mofetil, mycophenolate sodium or azathioprine) plus a corticosteroid (prednisone, prednisolone or methylprednisolone).(6, 7) Mycophenolate has largely replaced the less potent azathioprine in current clinical practice except in patients with serious adverse reactions to the former. Sirolimus (or the related drug everolimus) is generally not used in the early post-transplant period.

In renal transplant patients with good renal function, one of the three drugs in the initial triple therapy regimen may be discontinued post-transplant in order to minimize its long-term adverse effects. (6, 7) Thus, a patient presenting to the ED may be on only two anti-rejection medications. Corticosteroid is the most commonly withdrawn anti-rejection medication. In patients with chronically impaired allograft function, the nephrotoxic CNI may have been stopped and replaced with sirolimus or everolimus.(6) Rarely, one might encounter a renal transplant patient in whom all immunosuppressive medications have
been discontinued due to severe infection or malignancy. The currently approved maintenance immunosuppressive drugs are shown in Table 1.

Table 1. Commonly used maintenance immunosuppressive medications in current clinical practice

<table>
<thead>
<tr>
<th>Medication</th>
<th>Recommended Drug Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azathioprine (Imuran® or generic)</strong></td>
<td>Drug level monitoring not recommended</td>
</tr>
<tr>
<td><strong>Corticosteroids (Prednisone, Prednisolone or Methylprednisolone)</strong></td>
<td>Drug level monitoring not recommended</td>
</tr>
<tr>
<td><strong>Cyclosporine (Sandimmune®, Neoral™ or generic)</strong></td>
<td>Trough level: 250 to 400 ng/mL (initial) and 125 to 200 ng/mL (long-term)</td>
</tr>
<tr>
<td><strong>Everolimus (Zortress®)</strong></td>
<td>Trough level: 3 to 8 ng/mL</td>
</tr>
<tr>
<td><strong>Mycophenolate Mofetil (CellCept® or generic)</strong></td>
<td>Drug level monitoring not recommended</td>
</tr>
<tr>
<td><strong>Mycophenolate Sodium (Myfortic® or generic)</strong></td>
<td>Drug level monitoring not recommended</td>
</tr>
<tr>
<td><strong>Sirolimus (Rapamune® or generic)</strong></td>
<td>Trough level: 10 to 20 ng/mL (initial) and 5 to 15 ng/mL (long-term)</td>
</tr>
<tr>
<td><strong>Tacrolimus (Prograf® or generic)</strong></td>
<td>Trough level: 10 to 15 ng/mL (early) and 5 to 10 ng/mL (long-term)</td>
</tr>
</tbody>
</table>

In addition to the above mentioned maintenance drugs, anti-lymphocyte antibodies are used immediately after transplantation as induction therapy to prevent rejection (currently in >70% of renal transplant recipients in the United States), or as treatment of acute rejection unresponsive to initial therapy with high-dose intravenous methylprednisolone for 3 to 5 days.(8) If the renal transplant team requests the administration of intravenous methylprednisolone (250 to 1000mg/ dose) in the ED for presumed acute rejection, it should be remembered that such doses should be given over 30 to 60 minutes because
fatal cardiac arrhythmia has been reported with rapid bolus administration.\(^9\) Currently available anti-lymphocyte agents for induction therapy are rabbit anti-lymphocyte globulin (Thymoglobulin\(^\text{®}\)), horse anti-lymphocyte globulin (ATGAM\(^\text{®}\)), muromonab (OKT3\(^\text{®}\)), alemtuzumab (Campath\(^\text{®}\)), basiliximab (Simulect\(^\text{®}\)) and dacluzumab (Zenapax\(^\text{®}\)).\(^8\) The first four of these drugs can also be used for treatment of corticosteroid-resistant rejection.

The commonly encountered adverse effects of maintenance immunosuppressive medications are shown in Table 2.\(^6\)

### Table 2. Adverse effects of maintenance immunosuppressive medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>Macrocyclic anemia, leukopenia, thrombocytopenia, hepatotoxicity, pancreatitis</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Obesity, mooning of the face, diabetes mellitus, cataracts, acne, thinning of skin, bruising, gastro-duodenal ulceration/bleeding, hyperlipidemia, psychosis, osteoporosis/fracture, avascular necrosis of bone</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Reversible (dose and level-related) acute nephrotoxicity, chronic/progressive/irreversible nephrotoxicity, hyperkalemia, hypomagnesemia, hemolytic-uremic syndrome, hypertension, hyperlipidemia, diabetes mellitus, increased uric acid level ± gout, abnormal liver function tests, neurotoxicity (tremor, paresthesiae, cramps, headache, insomnia, seizure), hirsutism, gingival hyperplasia</td>
</tr>
<tr>
<td>Mycophenolate Mofetil</td>
<td>Nausea, vomiting, esophageal ulceration/dysphagia, heartburn, abdominal pain, loss of appetite/weight-loss, upper gastrointestinal ulceration/bleeding, colitis/diarhoea/lower gastrointestinal bleeding, anemia, leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Mycophenolate Sodium</td>
<td>Similar to Mycophenolate Mofetil (see above); gastrointestinal adverse effects may be less severe</td>
</tr>
<tr>
<td>Sirolimus/Everolimus</td>
<td>Anemia, leukopenia, thrombocytopenia, diarrhea, hyperlipidemia, oral ulcers, skin rash, localized /asymmetric edema, proteinuria, interstitial</td>
</tr>
</tbody>
</table>
Tacrolimus

- pneumonitis, delayed wound-healing, increased incidence of lymphocele, increased incidence/duration of delayed graft function
- Generally similar to Cyclosporine (see above) with the following differences: more diabetogenic and neurotoxic, cause alopecia rather than hirsutism, does not cause gingival hyperplasia

The emergency physician should also be aware of the clinically important drug-interactions involving anti-rejection medications which are shown in Table 3.(6)

Table 3. Clinically important drug interactions with immunosuppressive drugs

<table>
<thead>
<tr>
<th>Immunosuppressive Drug(s)</th>
<th>Drug(s) Causing Interaction</th>
<th>Mechanism and Result(s) of Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>Allopurinol</td>
<td>Azathioprine is metabolized by xanthine oxidase, the enzyme inhibited by allopurinol. Allopurinol, therefore increases azathioprine blood levels with an increased risk of azathioprine induced bone marrow suppression.</td>
</tr>
<tr>
<td>Cyclosporine, Tacrolimus, Sirolimus or Everolimus</td>
<td>Phenobarbital, Phenytoin, Carbamazepine, Rifampin, or Isoniazid</td>
<td>Potentiation of hepatic cytochrome P-450 enzyme system with increased metabolism and decreased blood level of immunosuppressive drug and resultant increased risk of rejection</td>
</tr>
<tr>
<td></td>
<td>Diltiazem, Verapamil, Amiodarone, Azole antifungals,* Macrolide antibiotics†</td>
<td>Inhibition of cytochrome P-450 decreases metabolism, causing increased blood levels and a higher incidence of known adverse drug effects, particularly a higher risk of cyclosporine or tacrolimus nephro- and neurotoxicity</td>
</tr>
<tr>
<td>Cyclosporine or Tacrolimus</td>
<td>Aminoglycosides, Iodinated radioccontrast, Amphotericin, Nonsteroidal anti-inflammatory drug</td>
<td>These nephrotoxic drugs may potentiate cyclosporine or tacrolimus nephrotoxicity. No change in metabolism or blood level of the immunosuppressive drug</td>
</tr>
</tbody>
</table>
**Cyclosporine**  | **HMG CoA-reductase inhibitors**  | Statin blood level increased by cyclosporine: increased risk of statin-induced rhabdomyolysis + acute kidney injury

*Keto-, Flu-, Vori- or Itroconazole

†Erythromycin and Clarithromycin. Azithromycin has only minimal drug interaction.

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**Approach to Acute and Chronic Renal and Urinary Tract Disorders in Renal Transplant Recipients**

The allograft and the urinary tract of the renal transplant patient can be affected by any of the disorders that occur in their native counterparts. Therefore, the emergency physician may encounter renal transplant recipients presenting with acute kidney injury ([AKI] previously referred to as acute renal failure), chronic kidney disease ([CKD] previously referred to as chronic renal failure), proteinuria/nephrotic syndrome, hematuria, urinary tract obstruction or urinary tract infection (UTI). Rejection is, of course, a unique disorder affecting only the kidney transplant. Renal dysfunction due to BK-Polyoma virus--associated nephropathy affects 5-10% of renal transplant patients but is very rare in native kidneys.

The same differential diagnostic approach traditionally used when evaluating AKI affecting the native kidneys is also applicable to the renal transplant patient: pre-renal, post-renal and intra-renal causes. The diagnosis of AKI requires an acute increase in the serum creatinine level of $\geq 0.3 \text{ mg/dL}$ over the most recently documented baseline level; smaller increases may be the result of random laboratory variation. After the exclusion of pre- and post-renal causes, the two common diagnostic considerations in the
renal transplant patients with AKI are acute rejection and acute CNI-nephrotoxicity. Elevation in SCr associated with a higher than therapeutic blood level of cyclosporine or tacrolimus favors the diagnosis of CNI-nephrotoxicity. A key point for the emergency physician to remember is that it is the trough level of cyclosporine or tacrolimus that is used in therapeutic monitoring. These drugs are administered every 12 hours and the trough level should be obtained in the 1 to 3 hour period immediately preceding the drug dose. Since the renal transplant recipient may come to the ED after having already taken the medication, the random level obtained on arrival in the ED may be elevated because it was drawn prior to the trough period. A low fractional excretion of sodium (FENa) in the urine supports the diagnosis of pre-renal azotemia in native kidney AKI. However, acute rejection and acute CNI-nephrotoxicity may also be associated with a low FENa, making this test less useful in the evaluation of post-transplant AKI. To decrease the risk of AKI, the intrinsically nephrotoxic drugs shown in Table 3 and iodinated radiocontrast should be avoided in renal transplant patients.

Evaluation of the allograft by ultrasonography is especially useful in the renal transplant patient presenting with AKI. Demonstration of new onset hydronephrosis suggests obstructive uropathy. Doppler ultrasonography helps in diagnosing renal arterial or venous occlusion as the cause of AKI.

The most common cause (65 to 70% of cases) of CKD in the RTR is the entity previously referred to as chronic rejection and currently called chronic allograft nephropathy (CAN) or interstitial fibrosis/tubular atrophy. This syndrome is characterized by a gradually
increasing SCr level and proteinuria over months to years. Recurrence of the original disease that caused ESRD and the uncommon development of *de novo* renal disease in the allograft account for the remainder of the cases of CKD in renal transplant patients.(13)

It is important to remember that microscopic or gross hematuria and UTI in the renal transplant patient may originate from the lower urinary tract, the native kidneys or the allograft.(14, 15) Thus, it is necessary to include both the native kidneys and the allograft when performing imaging studies to evaluate these disorders. Although the microbial spectrum causing UTI in this patient population is similar to that in the native urinary tract, the clinical presentation of UTI may be more severe post-transplant, especially during the first post-transplant year due to the higher dose of immunosuppressive medications during this period.(15) It should also be remembered that besides UTI, acute rejection may also cause pyuria in renal transplant recipients.(2) The current incidence of UTI in the first post-transplant year is 10 to 15%. Pyelonephritis affecting the allograft can cause severe AKI, and may be complicated by gas formation in the renal collecting system and urinary tract (emphysematous pyelonephritis, best demonstrated by computerized tomography).(16) In the initial treatment of severe UTI in a renal transplant recipient, a combination of two potent antibiotics intravenously (for example, vancomycin and a third-generation cephalosporin) should be used. Unless unavoidable, nephrotoxic drugs such as aminoglycosides and high-dose trimethoprim-sulfamethoxazole should not be used.
Table 4 summarizes the special considerations when evaluating a renal transplant patient with AKI.

**Table 4. Special Considerations in the Evaluation and Initial Treatment of Acute Kidney Injury (AKI) in Renal Transplant Recipients**

1. Any disorder (pre-renal, intra-renal and post-renal) that can cause AKI in the native kidneys can affect the transplant kidney.

2. After exclusion of other causes of AKI, acute rejection and acute calcineurin-inhibitor (CNI) nephrotoxicity are the major diagnostic considerations.

3. Elevated CNI (cyclosporine or tacrolimus) trough level in association with AKI supports the diagnosis of acute CNI nephrotoxicity.

4. Random CNI blood level drawn upon arrival in the ED may not be a trough level. Time of last intake of CNI should be ascertained.

5. Fractional excretion of sodium (FENa) in the urine has limitations when used in this patient population. Urinalysis, including microscopy of urinary sediment, is more useful.

6. Doppler ultrasonography of the kidney transplant is a very useful test in evaluating AKI. It helps to identify obstructive uropathy, peri-transplant fluid collection (urinoma, lymphocele, seroma/hematoma) and renal arterial or venous occlusion.

7. Unless unavoidable, prescription of nephrotoxic drugs (Table 3) and use of iodinated radiocontrast is not advisable.

8. When prescribing new drugs or changing the dose of existing drugs, the possibility of drug interactions involving immunosuppressive medications should always be considered (Table 3).

**Surgical Complications Related to the Kidney Transplant Operation**

A variety of surgical complications, most of them requiring prompt consultation with the transplant surgery team, may be encountered in the renal transplant patient.(3, 17)
1. **Generic post-operative complications**: Disorders that can complicate any type of surgery can also occur in the renal transplant patient. These include pulmonary atelectasis and pneumonia following general anesthesia, surgical wound infection, abdominal ileus, postoperative bleeding, venous thrombosis/pulmonary embolism, among others.

2. **Acute vascular occlusion**: Occlusion of the transplant renal artery or vein occurs in up to 8% of renal transplant patients. (3, 17) This catastrophe usually occurs in the first few weeks post-transplant and results in sudden onset oligoanuric AKI. Doppler ultrasonography is the most expeditious method of confirming the diagnosis, and prompt surgical intervention offers the only (albeit small) chance of salvaging the kidney transplant.

3. **Transplant renal artery stenosis**: Significant (> 50 to 70%) narrowing of the allograft renal artery has to be considered in the differential diagnosis of post-transplant hypertension and/or acute or chronic renal dysfunction. It has been reported in up to 10% of renal transplant recipients. (3)

4. **Bleeding from or near the kidney transplant**: This complication has been reported in 2-3% of renal transplant patients, usually in the early post-transplant period. (3, 5) Failure to achieve adequate hemostasis intra-operatively, initiation of anticoagulation for any indication post-operatively, bleeding following biopsy of the allograft and (rarely) severe acute rejection resulting in marked swelling/rupture of the allograft are
contributory factors. Presenting symptoms of allograft rupture include tenderness over the allograft, sudden hypotension, a drop in the hemoglobin level, AKI of the kidney transplant, and/or difficult to control hyperkalemia due to red cell lysis in the peri-transplant hematoma. Non-contrast computed tomography is the best diagnostic test, and significant peri-transplant bleeding requires prompt surgical intervention.

5. Urine leak (urinoma): Disruption of the ureteroneocystostomy anastamosis leads to urine leak into the pelvis. Urea, creatinine and water in the extravasated urine will be reabsorbed into the blood stream with resultant oliguria and azotemia. This complication usually occurs within the first month post-transplant with a reported incidence of 2 to 5%. The resultant peri-transplant fluid collection can be detected by ultrasonography. Percutaneous, ultrasound-guided aspiration of the fluid with demonstration of a markedly higher creatinine level in the aspirate compared to a simultaneously measured SCr level confirms the diagnosis of urinoma, and differentiates it from other peri-transplant fluid collections such as lymphocele (see below), hematoma or seroma. Unlike a urinoma, the aspirate creatinine level in these other types of fluid collections is nearly the same as the SCr level. Another method of confirming a urinary leak is isotopic renography with demonstration of persistent radioactivity over several hours in the peritransplant fluid collection due to extravasation of urine containing the intravenously injected radioisotope.

6. Peri-transplant lymph collection (lymphocele): This complication occurs in 5 to 15% of renal transplant patients usually within the first 3 months post-transplant. It
results from persistent leakage from pelvic lymphatics severed during the transplant operation. Small lymphoceles may be asymptomatic and detected incidentally by ultrasonography. Larger lymphoceles may cause local pain and/or fullness, increase in the SCr level by extrinsic pressure on the transplant ureter, pressure on the bladder with urinary frequency and lower extremity edema on the side of the kidney transplant due to pressure on the iliac veins. Compression by lymphocele may cause iliac venous thrombosis and, very rarely, partial or complete renal arterial occlusion. Percutaneous, ultrasound-guided external drainage is the initial treatment for patients with symptomatic lymphoceles.

7. Urinary tract obstruction in the renal transplant recipient: Obstructive uropathy occurs in 3 to 6% of renal transplant patients.(3) During the first three post-transplant months, this complication is usually caused by either technical problems at the ureteroneocystostomy, extrinsic compression of the ureter by a lymphocele, occlusion of the ureter or Foley catheter by blood clots in patients with gross hematuria or inability to empty the bladder (caused by the prostate or neurogenic bladder). Beyond the first three months, obstruction is the result of ureteric stenosis due to ischemia or scarring following episodes of rejection, or inability to empty the bladder because of the disorders mentioned above. Elevation of SCr associated with ultrasonographic demonstration of new onset or worsening of preexisting hydronephrosis is strongly suggestive of obstructive uropathy. Percutaneous nephrostomy with external drainage of urine is the preferred initial step in treating obstructive uropathy in this patient population.
8. **Bleeding following biopsy of the kidney transplant**: Biopsy of the kidney transplant for evaluation of renal dysfunction is performed mostly as an ambulatory procedure in which the patient is sent home after a few hours of observation. Although uncommon, this procedure may be complicated by bleeding. Such a patient may return to the ED with pain over the renal allograft, gross hematuria, hypotension, fall in the hemoglobin level and/or AKI. Computerized tomography identifies peri-transplant bleeding better than ultrasonography. Blood transfusions and embolization of the bleeding vessel by allograft angiography may be required.

9. **Lower quadrant abdominal pain at the site of the kidney transplant**: This is a common complaint in this patient population. Common causes of this complaint are shown in Table 5. It is important to remember that the pain may be unrelated to the allograft and causes of right or left lower quadrant abdominal pain in the general population should also be considered in the differential diagnosis.

| Table 5. Causes of lower quadrant abdominal pain at the site of the kidney transplant |
|------------------------------------------|------------------------------------------|
| **Transplant-Related**                  | **Transplant-Unrelated**                |
| 1. Severe acute rejection                | 1. Acute appendicitis                   |
| 2. Transplant pyelonephritis            | 2. Diverticulitis                      |
| 3. Pressure from large lymphocele,      | 3. Ischemic colitis                    |
|   urinoma or peri-transplant hematoma   |                                          |
| 4. Transplant wound infection/peri-      | 4. Infectious or inflammatory bowel     |
|   transplant infection                  |   disease                              |
| 5. Chronic, recurrent incisional pain*  | 5. Ovarian and pelvic inflammatory     |
|                                          |   disorders                            |
Fever is a challenging complaint that frequently leads renal transplant recipients to seek evaluation in the ED. Signs and symptoms of infection may be partially masked by immunosuppression. Additionally, the risk of opportunistic infections and the potential for a fulminant course complicate the diagnostic and therapeutic approach to fever in these patients. It should be remembered that these patients are more susceptible to severe sepsis, multilobar pneumonia and meningitis compared to the general population. It is useful to consider the time elapsed after transplantation when a renal transplant patient presents with fever (Table 6).

Table 6. Infectious risk based on time post-transplant*

<table>
<thead>
<tr>
<th></th>
<th>0-1 Month</th>
<th>1-6 Months</th>
<th>&gt; 6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nosocomial</strong></td>
<td>C. Difficile colitis</td>
<td><strong>Bacterial</strong></td>
<td><strong>Community-Acquired</strong></td>
</tr>
<tr>
<td></td>
<td>VRE, MRSA</td>
<td>Pneumococcus, Staphylococcus,</td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td>Candida</td>
<td>gram-negatives, Legionella</td>
<td>Urinary tract infections</td>
</tr>
<tr>
<td><strong>Post-surgical</strong></td>
<td>Wound infections</td>
<td><strong>Fungal</strong></td>
<td><strong>Fungal</strong></td>
</tr>
<tr>
<td></td>
<td>Anastamotic leaks</td>
<td>Cryptococcus, Aspergillus, PCP</td>
<td>Aspergillus, Nocardia</td>
</tr>
<tr>
<td><strong>Donor-derived</strong></td>
<td>West Nile virus</td>
<td><strong>Viral</strong></td>
<td><strong>Atypical molds</strong></td>
</tr>
<tr>
<td></td>
<td>HSV, HIV, HCV</td>
<td>Influenza, CMV, EBV, VZV</td>
<td>CMV colitis/retinitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BK virus, HCV, HBV</td>
<td>HBV, HCV, HSV, EBV</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td><strong>Other</strong></td>
<td><strong>Latent viral</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toxoplasmosis, Mycobacterial</td>
<td>CMV colitis/retinitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C. Difficile colitis, Strongyloides</td>
<td>HBV, HCV, HSV, EBV</td>
</tr>
</tbody>
</table>

* Adapted from Fishman.(21)  VRE: Vancomycin resistant enterococcus faecalis; MRSA: methicillin resistant Staphylococcus aureus; HSV: Herpes simplex virus; HIV: Human immunodeficiency virus; HCV: Hepatitis C virus; PCP: Pneumocystis jirovecii (carinii); CMV: Cytomegalovirus; EBV: Epstein-Barr virus; VZV: Varicella zoster virus; HBV: Hepatitis B virus
These patients carry the highest risk of opportunistic infections during the second through the sixth month following transplant. During the first month after transplant, nosocomial and post-operative infections such as wound infection, line-sepsis and UTIs may occur, but are infrequent. Early opportunistic infections are rare since the full effect of immunosuppression is not yet present. Also encountered in the first month rarely are donor-derived (transmitted through the allograft) infections such as Hepatitis C virus or West Nile virus. Between thirty days and six months post-transplant, a wide spectrum of opportunistic infections reach their highest incidence in this patient population.\(^{(21)}\) The prevalence of specific opportunistic pathogens varies geographically, and consultation with the transplant team can aid emergency physicians to narrow down the diagnostic possibilities in patients they encounter.

Cytomegalovirus (CMV) is a significant opportunistic pathogen in all types of transplant recipients. Despite universal prophylaxis with ganciclovir or valganciclovir, symptomatic CMV infection still occurs in 10% to 25% of renal transplant patients.\(^{(22)}\) CMV infection may present as CMV disease, characterized by high fever, elevated liver enzymes, and pancytopenia. Tissue-invasive CMV infection (pulmonary, gastrointestinal, or central nervous) represents the more severe spectrum of CMV disease. The most expeditious method to confirm the diagnosis within 24 to 48 hrs is the polymerase chain reaction (PCR) assay for CMV-DNA in the blood. Use of routine antimicrobial prophylaxis has decreased but not eliminated the chance of Pneumocystis or CMV infection.
The ED evaluation of the febrile renal transplant patient should include complete blood count and differential, SCr, urinalysis, urine and blood cultures, and chest radiograph. Additional tests (especially CMV-PCR and liver function tests) may be necessary in the appropriate clinical setting. Consideration of non-infectious causes of fever is also warranted in these patients, particularly severe acute rejection, the administration of anti-lymphocyte antibodies, and post-transplant lymphoma.(21) Post-transplant lymphoma may initially present as an infectious mononucleosis-like illness.(23)

Past the first six months, community-acquired infections predominate in renal transplant recipients. By this time, in the majority of patients the immunosuppressive regimen has been tapered to maintenance doses thus decreasing the risk of opportunistic infections. However, opportunistic infections may still occur, especially if a recent rejection episode has required intensified anti-rejection therapy.

In the first year post-transplant, most febrile renal transplant patients will require hospitalization due to the potential for a fulminant course, and the risk of nosocomial or opportunistic infections and rejection. A lower threshold for admission and observation is still warranted in more long-term patients, but outpatient management of milder infectious processes may be possible in consultation with the transplant team.

**Cardiovascular and Hypertension-Related Disorders in Renal Transplant Recipients**
Atherosclerotic cardiovascular disease is the leading cause of death in renal transplant patients, accounting for approximately 40% of post-transplant mortality. In comparison to an age-matched general population, these patients carry a three to five-fold higher risk of cardiovascular disease. Even prior to transplantation, chronic kidney disease is associated with accelerated atherogenesis. High prevalence of diabetes (40 to 50%), hypertension (up to 90%) and hyperlipidemia (50 to 60%) are major contributors to the increased cardiovascular risk. No matter how atypical the presentation and even in patients younger than 40 years, a high index of suspicion for an acute coronary syndrome is justified in the transplant population.

The diagnostic and therapeutic approach to cardiovascular disorders in renal transplant recipients is the same as in the general population. There are no unique contraindications to anticoagulation or the use of any parenteral or oral antihypertensive agents in these patients. However, diltiazem, verapamil and amiodarone inhibit the hepatic cytochrome P-450 enzyme system and can lead to cyclosporine or tacrolimus nephrotoxicity due to decreased metabolism of these immunosuppressants. Brief use of these agents as an emergent anti-arrhythmic agent is acceptable, but continuing long-term outpatient use requires coordination with the transplant team to monitor immunosuppressive drug levels and adjust dosing downward as necessary.

**Renal Transplant Recipients Presenting with Respiratory Complaints**

When evaluating respiratory symptoms, the risk of an opportunistic pneumonia and possibility of a more fulminant course separate the renal transplant patient from the
general population. Factors that influence their evaluation and treatment in the ED include the time period since transplantation, severity of illness and radiographic appearance.

Postoperative, non-opportunistic pneumonia may occur in the first post-transplant month. Opportunistic infections become a significant problem past the first month and must be considered in the evaluation of respiratory symptoms. The pattern of pulmonary infiltrate can offer clues to possible etiology. Lobar consolidation is suggestive of bacterial pneumonias caused by organisms such as Pneumococcus or Legionella. A bilateral interstitial pattern points to Pneumocystis or CMV pneumonia. Additionally, interstitial pneumonitis associated with sirolimus therapy should be considered. Nodular or cavitating lesions suggest fungal infections such as Aspergillus, Cryptococcus, or Histoplasma. Even in the setting of mild symptoms, findings suggestive of fungal infection require aggressive investigation due to the risk of significant morbidity.

Computerized tomography is frequently necessary in evaluating pulmonary complaints in transplant patients. Non-diagnostic radiographs may fail to rule-out the early stages of bacterial pneumonia. Tuberculous, fungal, Pneumocystis, and CMV pneumonias can present with sub-acute symptoms and unimpressive radiographs. The risk of these pathogens is greatest in months one through six post-transplant and during periods of intensified immunosuppression. Pneumocystis may present with hypoxemia, dyspnea, and cough with subtle or absent physical and radiographic findings. There should be a high
index of suspicion for the diagnosis of tuberculosis because its incidence is increased in immunosuppressed patients.

The threshold for hospital admission of renal transplant patients with suspected pulmonary infection should be low due to the potential for a rapidly deteriorating course. Unless tuberculosis is suspected, strict isolation precautions are not required. Nevertheless, many institutions elect to place hospitalized transplant patients in private rooms for the first 6 to 12 months post-transplant to decrease the risk of nosocomial infections.

Because of the risk of unusual opportunistic and resistant pathogens, every attempt should be made to obtain adequate blood and sputum culture specimens before initiating empiric antimicrobial therapy. However, empiric therapy should be initiated promptly, particularly during the first 6 months post-transplant as these immunosuppressed patients can deteriorate rapidly. Treatment for a community-acquired pneumonia or healthcare-associated pneumonia should be initiated according to established guidelines. Patients within the first six months of transplant require this same treatment but warrant additional consideration for antimicrobials targeted at opportunistic organisms.

The macrolide antibiotics are commonly used to treat respiratory infections, but can have significant pharmacological interaction in transplant patients. The majority of macrolides inhibit the hepatic enzymes that metabolize cyclosporine, tacrolimus, and sirolimus. Therefore, it is important to monitor the blood level and reduce the dose of these...
immunosuppressants if a macrolide antibiotic is selected. Azithromycin is preferred because it is the macrolide least likely to affect the metabolism of these immunosuppressants.(27)

**Renal Transplant Recipients Presenting with Gastrointestinal Complaints**

Just as immunosuppressants blunt the immune system’s response to various microbes, these medications (corticosteroids in particular) may also mask the peritoneal response to significant intra-abdominal pathology. The clinical presentation of serious abdominal conditions such as acute cholecystitis, visceral perforation, diverticulitis and bowel infarction may be muted.(34) An intra-abdominal catastrophe cannot be excluded because abdominal pain is mild and guarding and/or rebound tenderness are absent. The care of renal transplant patients with abdominal pain requires a low threshold for ultrasound or computerized tomography imaging and surgical consultation.

There are a broad range of gastrointestinal/hepatobiliary/pancreatic problems that are encountered in transplant patients. The two major causes of these disorders are direct adverse effects of immunosuppressants and a variety of infections which occur in immunosuppressed patients. Table 7 summarizes these disorders.

**Table 7. Gastrointestinal disorders in renal transplant recipients due to infectious or drug-related complications.**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Infectious</th>
<th>Drug-related</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Pathogens</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral ulcers, plaques</strong></td>
<td>Candida, HSV</td>
<td>Sirolimus</td>
</tr>
<tr>
<td><strong>Esophagitis</strong></td>
<td>Candida, HSV, CMV</td>
<td>Mycophenolate Mofetil</td>
</tr>
<tr>
<td><strong>Gastroduodenitis, upper gastrointestinal ulceration/bleeding</strong></td>
<td>CMV infection, EBV-related gastrointestinal lymphoma</td>
<td>Mycophenolate, Mofetil, corticosteroids</td>
</tr>
<tr>
<td><strong>Diarrhea, lower gastrointestinal ulceration/bleeding</strong></td>
<td>CMV infection, Microsporidium, Cryptosporidium, EBV-related intestinal lymphoma</td>
<td>Mycophenolate mofetil, Sirolimus</td>
</tr>
<tr>
<td><strong>Hepatic dysfunction</strong></td>
<td>CMV, EBV, Hepatitis C and B</td>
<td>Cyclosporine, Tacrolimus</td>
</tr>
<tr>
<td><strong>Pancreatitis</strong></td>
<td>CMV</td>
<td>Azathioprine</td>
</tr>
</tbody>
</table>

*HSV: Herpes simplex virus; CMV: Cytomegalovirus; EBV: Epstein-Barr virus

**Renal Transplant Recipients Presenting with Neurological or Psychiatric Problems**

New onset headache, seizure, or change in mental status in a renal transplant patient may be the result of very serious disorders such as meningitis, encephalitis or neoplasm. Such symptoms warrant prompt imaging and lumbar puncture. The incidence of an opportunistic central nervous system (CNS) infection approaches 10% in this population, particularly within the first six months post-transplant. Common pathogens include Cryptococcus neoformans, Mycobacterium tuberculosis, and Listeria monocytogenes. Additional pathogens to consider are CMV, Herpes simplex, JC-Polyoma and West Nile viruses, and Toxoplasma gondii. Because of the masking effect of immunosuppression, fever, leukocytosis and meningismus may be absent in these patients. Hence, the threshold for cerebrospinal fluid (CSF) analysis in these patients
should be low. It should also be remembered that despite severe meningoencephalitis, CSF chemical abnormalities and pleocytosis may be equivocal. The most common CNS neoplasm in renal transplant recipients is post-transplant lymphoma.\(^{(38)}\)

Immunosuppressant medications are also associated with neurological adverse effects. CNIs are known to cause headache, insomnia, tremors, paresthesiae affecting the hands/feet, seizures and global encephalopathy.\(^{(39)}\) Tacrolimus is more neurotoxic than cyclosporine. Severe encephalopathy may also be due to neurological toxicity of drugs such as acyclovir, penicillins and cephalosporins, especially when given to patients with impaired allograft function. Corticosteroid psychosis may also underlie alterations in mood in transplant recipients. Lastly, the prevalence of depression and risk of suicide are higher among renal transplant patients compared to the general population.\(^{(40)}\)

**Hematologic Disorders in Renal Transplant Recipients**

Medication-associated cytopenias are common in renal transplant recipients.\(^{(41)}\) Additionally, chronic transplant dysfunction may cause anemia of chronic kidney disease. The prevalence of anemia approaches 21% at one year and 36% at three years following transplantation.\(^{(42)}\) Opportunistic viral infections, particularly CMV and parvovirus, are also associated with cytopenias. Lastly, common prophylactic medications such as trimethoprim-sulfamethoxazole, ganciclovir, and valgancyclovir can all be associated with cytopenias. When blood product transfusions are required for symptomatic anemia,
the use of leukocyte-poor blood is recommended for transplant patients to decrease the risk of sensitization to HLA-antigens.(22)

Hemolytic-uremic syndrome (HUS) is an emergent condition to consider when a renal transplant patient presents with the triad of anemia, thrombocytopenia, and AKI. History of ESRD secondary to native kidney HUS, cyclosporine, tacrolimus or sirolimus therapy, severe acute vascular rejection, and CMV infection are the risk factors for post-transplant HUS.(43) Diagnostic clues include elevated lactate dehydrogenase, low haptoglobin levels and the presence of schistocytes on a peripheral blood smear.

Leukocytosis and erythrocytosis can also occur in renal transplant patients. The primary cause of non-infectious leukocytosis is de-margination of leukocytes by corticosteroids. Band forms should be absent with de-margination, and their presence suggests infection. Up to 20% of renal transplant recipients will have erythrocytosis in the first year following transplant, and in half of these patients, erythrocytosis may persist long-term.(44) Erythrocytosis predisposes post-transplant patients to thromboembolic events, and may cause chronic dizziness and headaches.

Table 8 summarizes the common hematological disorders encountered in renal transplant recipients.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Special considerations</th>
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</table>

Table 8. Common hematologic disorders and special considerations in renal transplant recipients
### Cytopenias

- CMV or Parvovirus infection
- Drug effects: Mycophenolate Mofetil, Sirolimus, Everolimus, Azathioprine, Ganciclovir, Valgancyclovir, Trimethoprim-Sulfamethoxazole

### Hemolytic-uremic Syndrome (HUS)

- Recurrence of native kidney HUS, severe vascular rejection, CMV infection
- Drug effects: Cyclosporine, Tacrolimus, Sirolimus

### Leukocytosis

- Corticosteroids

### Erythrocytosis

- Endogenous erythropoietin (source: native kidney > allograft), and other factors

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**Renal Transplant Recipients Presenting with Musculoskeletal and Articular Complaints**

Renal transplant recipients are at increased risk for a number of musculoskeletal and articular emergencies. Corticosteroids accelerate osteoporosis resulting in an increased risk of fractures. For unclear reasons, the most common site of fractures in renal transplant recipients is the foot. Unexplained foot pain with or without trauma may well be the result of a fracture. Avascular necrosis with hip and/or knee pain occurs in up to 3.5% of renal transplant recipients and may require magnetic resonance imaging for diagnosis in its early stages. Pending imaging, immobilization for presumed fracture may be appropriate.

Acute gout is common in renal transplant patients on CNIs. These medications reduce renal uric acid excretion and cause hyperuricemia. In the diagnostic evaluation of arthritis in renal transplant recipients, arthrocentesis is important to differentiate septic arthritis from gout. The therapeutic approach also has a few caveats: nonsteroidal anti-
inflammatory drugs may cause AKI/ARF, and colchicine can interact with cyclosporine and cause leukopenia, hepatic dysfunction, and rhabdomyolysis.(47) In this population, corticosteroids and alternative analgesics are better therapeutic choices for gout.

Long-term corticosteroid use may cause proximal muscle weakness of the limbs secondary to steroid myopathy. Corticosteroids and tendon calcification secondary to hyperparathyroidism contribute to increased risk of tendon rupture in this patient population.(48) Quinolone antibiotic use may further increase this risk.(2) Pain and swelling over common sites of rupture such as the Achilles or quadriceps tendon should prompt soft-tissue ultrasonography or magnetic resonance imaging for rupture even in the setting of minor trauma. Following complete discontinuation of corticosteroids, renal transplant patients may present with polymyalgia and polyarthralgia which may respond to reinstitution of a small dose of corticosteroid.(2)

Table 9 shows the special considerations in the evaluation of musculoskeletal and articular problems in renal transplant recipients.

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot pain</td>
<td>Foot fractures are common and history of trauma may be lacking</td>
</tr>
<tr>
<td>Hip pain</td>
<td>Increased risk of avascular necrosis due to corticosteroid use</td>
</tr>
<tr>
<td>Acute arthritis</td>
<td>Increased risk of gout on CNI, but care should be taken to rule-out a septic joint. NSAIDs and colchicine use not advisable</td>
</tr>
</tbody>
</table>
Common Electrolyte Disorders Encountered in Renal Transplant Recipients

Potassium and magnesium abnormalities are common among renal transplant recipients. Patients on cyclosporine and tacrolimus frequently require magnesium replacement secondary to chronic renal magnesium wasting. The CNIs also reduce urinary potassium excretion, resulting in hyperkalemia. Additional medications that contribute to hyperkalemia in these patients are trimethoprim-sulfamethoxazole, ACE-inhibitors, and angiotensin-II-receptor blockers.

Hypercalcemia and hypophosphatemia occur in 5% to 10% of renal transplant patients due to persistence of secondary hyperparathyroidism in the setting of good allograft function. Lastly, normal anion gap renal tubular acidosis may be noted in patients with allograft dysfunction.

Endocrine Complications in Renal Transplant Recipients

New-onset diabetes mellitus occurs in approximately 25% of patients within three years of renal transplantation. Both corticosteroid and CNI (particularly tacrolimus) use contribute to this increased risk of diabetes. Symptoms of polyuria, polydipsia and weight loss should prompt testing for diabetic emergencies in renal transplant recipients. Diabetic ketoacidosis occurs in approximately 8% and hyperosmolality in 3% of renal
transplant patients who develop post-transplant diabetes mellitus.(51) The treatment of these diabetic complications is not different from that of non-transplant patients.

Acute adrenal insufficiency is a significant concern in critically ill renal transplant recipients. The majority of these patients receive corticosteroids for some period of time for immunosuppression with resultant suppression of their pituitary-adrenal axis. Stress-dose corticosteroid coverage (intravenous hydrocortisone 100 mg every 8 hours) is required in the critically ill renal transplant patient unless steroid therapy had been discontinued more than 6 to 12 months earlier.(52)

**The Next Five Years**

Currently there are approximately 90,000 patients wait-listed for kidney transplantation in the US.(1) With the increasing global incidence/prevalence of ESRD due to a combination of aging of the population and the epidemic of obesity and diabetes, the demand for kidney transplantation is bound to increase. If the availability of organs for transplantation increases, the number of renal transplant recipients and ED visits by these patients will likewise rise. HIV infection was, until recently, considered an absolute contraindication to kidney transplantation. Nevertheless, the increasing success of anti-retroviral therapy has cleared the way for carefully selected HIV-positive ESRD patients to be accepted for transplantation.(53) This high risk population will be more likely to seek care in the ED.
Several new and potent immunosuppressive medications and monoclonal antibodies are likely to be approved in the coming years (example: Belatacept) and may result in a higher incidence of emergent adverse effects, including drug interactions, infection and malignancy. The pattern of post-transplant infections for which a renal transplant patient may seek care in the ED may subsequently change with time as new immunosuppressant medications are introduced and patients with more comorbidities become renal transplant recipients. Finally, transplant tourism (patients travelling to countries where commercial transplantation using paid live donors is practiced) is increasing.(54) These patients may present to the ED with uncommon infections acquired abroad.

**Conclusion**

Renal transplant patients represent a growing and challenging ED patient population. Careful consideration of the time since transplantation and broad differential diagnosis can aid the emergency physician in the evaluation and management of these individuals when presenting for acute care. Early consultation with the transplant team can be invaluable in assuring that renal transplant recipients receive quality care in the emergency department.

**References**


Principles of dialysis therapy

Pharmacists must be aware of in-center, home, and peritoneal dialysis and consider the different techniques and the potential benefits and risks associated with each. The choice of dialysis modality depends on various factors, including patient preferences, comorbidities, and access to healthcare services.

Introduction and epidemiology

The end-stage renal disease (ESRD) patient population is increasing significantly worldwide. The prevalence of ESRD has more than doubled over the past decade, reflecting the growing burden of chronic kidney disease globally.

The end-stage renal disease patient is often referred to a nephrologist for initial management and a multidisciplinary approach to care. The nephrologist, in collaboration with other healthcare providers, will assess the patient's condition and determine the most appropriate treatment plan.

Principles of dialysis therapy

The goal of dialysis therapy is to remove waste products and excess fluids from the bloodstream and maintain electrolyte and acid-base balance. This is achieved through removal of metabolic waste products, including urea and creatinine, and excess water, sodium, and potassium.

In-center dialysis

In-center dialysis typically involves hemodialysis, which is performed in a dialysis unit under the supervision of a nephrologist or dialysis nurse. The process involves the use of a dialysis machine to filter blood, remove waste products, and regulate electrolyte levels.

Home dialysis

Home dialysis can be performed using either peritoneal dialysis or hemodialysis at home. Peritoneal dialysis involves the use of a dialysis solution that is instilled into the peritoneal cavity to remove waste products from the body. Hemodialysis at home follows a similar process to in-center dialysis but is performed at home.

Peritoneal dialysis

Peritoneal dialysis is a home dialysis modality that involves the use of a dialysis solution that is instilled into the peritoneal cavity and allowed to dwell for a period. This process is repeated several times a day. Peritoneal dialysis is generally preferred among patients who are on chronic dialysis and prefer the flexibility of home dialysis.
Problems and Blood Pressure-Related Management of the Dialysis Patient Presenting with Clear Pain

The end-stage renal disease patient on dialysis...
The end-stage renal disease pattern on discharge.

The prevalence of hypertension in the diabetic patient may indicate chronic renal disease. Hypertension, which is a common problem occurring in approximately 10% of patients, is a major cause of morbidity and mortality in patients with diabetes. Effective management of hypertension, including lifestyle modifications and medication, is crucial to improving outcomes in diabetic patients.

Hypertension

Hypertension is a common problem that occurs in diabetic patients. Effective management of hypertension is crucial to improving outcomes in diabetic patients.

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Syndrome

Syndrome
In dialysis patients due to hyperkalemia and hypocalcemia are common reasons.

4. Serum calcium levels are monitored closely in patients undergoing dialysis due to their increased risk of hyperkalemia and hypercalcemia.
5. Serum potassium levels are also monitored closely in patients undergoing dialysis due to their increased risk of hypercalcemia and hyperkalemia.

In conclusion, hyperkalemia and hypocalcemia are common in dialysis patients and require close monitoring and management to prevent complications.
The end-stage renal disease patient on dialysis

**Disorders in dialysis patients**

**Commonly encountered add-base and electrolyte...

[Syndrome] [11]

**Additives**...
Special Considerations in the Management of...

[Page torn, text incomplete]
Emergencies Related to Intradialytic Accidents
In patients who have not been taking medication for 3 days, the following medications should be considered for 50% reduction in the dosage of anti-epileptic drugs:

1. Carbamazepine (Carbatrol, Tegretol)
2. Phenobarbital (Luminal)
3. Phenytoin (Dilantin)
4. Lamotrigine (Lamictal)
5. Levetiracetam (Keppra)

*Note: The dosage reductions should be made under the supervision of a healthcare provider who is familiar with the patient's medical history and current condition.*


Department of Cardiovascular Medicine

The end-stage renal disease patient on dialysis...number of ESRD patients.

- The good economic of obesity and depressive individuals reduce the need for dialysis.
- The economic impact in the age of case of ESRD and improved outcomes.

However, the following outcomes may mitigate these favorable outcomes:

- The economic impact in the age of case of ESRD and improved outcomes.

The next five years...


References...