

CHAPTER 6

Implementing Patient Care Management: Acute and Chronic Care of the Kidney or Liver Transplant Recipient

*Robert E. Dupuis, Pharm.D., BCPS,
David Taber, and Amy Fann
School of Pharmacy
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina*

COPYRIGHT©2003 Fujisawa Healthcare, Inc. The right to photocopy this publication is granted to the recipient solely for distribution to and use by members of recipient's organization (photocopies of the examination contained in this publication will be accepted for purposes of obtaining continuing education credits). All other rights are reserved by Fujisawa Healthcare, Inc. and any other reproduction, distribution or use of any portion of this publication without the express written permission of Fujisawa Healthcare, Inc. is prohibited

EDITORIAL BOARD

All manuscripts undergo peer review and extensive editorial review.

Administrative Editor:

Karen Durrant, R.Ph
Manager, Continuing Education
Fujisawa Healthcare, Inc.
Deerfield, Illinois

Guest Editor:

Roy First, M.D.
Director, Medical Affairs
Fujisawa Healthcare, Inc.
Deerfield, Illinois

INSTRUCTIONS FOR OBTAINING CONTINUING EDUCATION CREDITS:

To obtain continuing education credits, please follow the instructions for electronic test submission. A score of 70% is required for certification. Participants will receive immediate feedback on the results of their exam. Those participants who successfully complete the program (passing grade of 70% or greater) will receive their statement of credit by mail within four weeks. Should you score less than 70%, no statement will be mailed. Note: All testing is electronic.

Fujisawa Healthcare, Inc. is approved by the American Board of Transplant Coordinators as a provider of continuing education.

003-010-00-009-CO1
2.0 Category 1 CEPTC



Fujisawa Healthcare, Inc. is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education.

332-000-03-106-H01
2 Contact Hours



This information is not intended as an endorsement of, or as a recommendation of, any Fujisawa Healthcare, Inc. product mentioned in this material.

 **Fujisawa**

New Medicines for New Times

GOALS/OBJECTIVES

Upon completion of this continuing education activity, participants should be able to:

- Define the role of the pharmacist and other health care professionals in the postsurgical care of a transplant patient
- Discuss the necessary mechanisms required to ensure a seamless transition from in-hospital care to the community setting
- Implement patient care models for the ongoing monitoring and care by pharmacists and other providers in acute, ambulatory, clinic, and community settings
- Identify the uses and benefits of data collection forms as a key component of a patient care model

INTRODUCTION

The best approach to the provision of care for the transplant recipient involves a multidisciplinary team that includes physicians, nurses, coordinators, dietitians, physical and occupational therapists, social workers, psychologists, and pharmacists. Each member of the team plays a vital role in ensuring optimal care to transplant patients in both institutional and community settings. It is the goal of this discussion to provide pharmacists and other clinically oriented members of the health care team with the knowledge and understanding of how to provide the most beneficial long-term care to transplant patients, once they leave the hospital and return to the community.

This review will include a brief discussion of acute care issues, but the main focus will be on chronic care after initial hospitalization. This includes long-term immunosuppressive strategies and infections. Long-term complications—such as osteoporosis, malignancy, diabetes, recurrence of disease, and chronic rejection—are also presented. Additionally, other considerations unique to the care of transplant patients will be mentioned. These include immunizations, potential drug interactions, nonprescription medication and dietary supplement

use, and patient medication nonadherence issues. Finally, guidance on the development of patient care plans and reimbursement strategies for pharmacists and allied health professionals providing care to these patients will be addressed.

ACUTE CARE

The immediate postoperative period in abdominal organ transplantation presents multiple therapeutic challenges and potential complications. The most common problems are graft dysfunction, electrolyte abnormalities, and infection. Assessment, prevention, and management differ somewhat between kidney and liver transplant patients as they exhibit different pathophysiology, both before and after transplantation. Much of the immediate post-transplantation care occurs in the intensive care unit (ICU) setting, particularly following orthotopic liver transplantation. Time spent in the ICU varies from less than 1 day for kidney transplants to several days for liver transplants.

Monitoring of Graft Function Immediately After Transplantation

Within the hours and days immediately following liver and kidney transplantation, monitoring of graft function plays a critically important role in postoperative care. Clinical laboratory tests, appearance and volume of urine and various surgical drain outputs, ultrasonography, nuclear medicine tests, and if necessary, biopsy, all aid in the clinician's judgment of the new graft's function.

Survival of the liver transplant patient depends on early graft function, since extracorporeal hepatic replacement devices are not standard therapy at this time. Assessment of the liver graft function begins shortly following reperfusion. Once stabilized and in the ICU, the physical examination of a patient with a functioning liver should reveal recovery of consciousness within approximately 12 hours following surgery. Laboratory evaluation shows a characteristic elevation of liver function tests with aminotransferases in the 1000s, and bilirubin concentrations remaining elevated. Steady decline of these values should begin within

2 to 4 days. As measures of the new liver's synthetic function, prothrombin time (PT) and partial thromboplastin time (PTT) also should begin to normalize within this time period. Since a functioning liver allograft aids the body in maintaining blood glucose concentrations through gluconeogenesis, hypoglycemia raises concern that the liver is not functioning well, unless the patient is on medications that can lower blood glucose levels. As liver function continues to improve and metabolic processes resume, electrolytes such as magnesium and phosphorus may require replacement.

Diagnosis of vascular complications from liver transplantation occurs most often through duplex ultrasonography. Ultrasound depicts blood flow in the hepatic artery, hepatic vein, and portal vein. Fluid collections surrounding the liver also can be visualized through ultrasound. Although interpretation of these tests is beyond the scope of this review, they are important in determining whether the liver graft is functioning properly. If the ultrasound shows decreased blood flow through these vessels, therapeutic options include pharmacotherapy, return to the operating room for restoration of blood flow, or, in the case of primary graft nonfunction, retransplantation. In a hemodynamically stable patient, low-intensity heparinization is sometimes instituted to prevent thrombosis around anastomotic sites created during the transplant surgery. In addition, nitroglycerin and diltiazem are sometimes employed to improve blood flow. Liver edema due to volume overload may be another cause of decreased blood flow. Adequate diuresis using a loop diuretic such as furosemide, and conservative fluid administration should be employed to prevent this occurrence.

Complications related to the biliary system — usually bile leaks or biliary strictures — occur in approximately 10% to 12% of patients. Bile leaks usually occur early after transplantation and involve anastomotic sites. Symptoms of a bile leak include fever and right upper quadrant pain. If a bile

collection develops around the leak it can cause obstruction of the bile duct around the affected site. Laboratory evidence of a bile leak includes elevation of bilirubin, gamma-glutamyltransferase (GGT), and alkaline phosphatase (AP).

In contrast to the liver transplant patient, delayed graft function is more common in renal transplantation patients, necessitating reinstitution of hemodialysis. Despite the immediate necessity for hemodialysis, the patient's surgery usually results in a functioning renal allograft. Patients with a functioning graft should begin having good urine output within hours of transplantation. Urine output may vary tremendously from patient to patient in the first 24 hours postoperatively. Appropriate fluid replacement is critical. With dramatic diuresis, electrolytes (i.e., potassium, calcium, magnesium, phosphorus) must be monitored frequently for any abnormalities. Should repletion be required, administration of potassium and magnesium should be approached in a conservative manner, as renal function is still not optimal. In a normally functioning renal allograft, serum creatinine will start falling soon after surgery. Delayed graft function occurs in 8–50% of cadaveric renal transplant patients, most commonly resulting from acute tubular necrosis (ATN). Delayed graft function is defined as the need for dialysis in the postoperative period. Other definitions have included the failure of serum creatinine to fall below 4 mg/dL or by 30% of the pre-transplant value within the first 48 hours. Pharmacologic strategies to decrease the amount of time the renal allograft undergoes ATN include administration of calcium channel blockers, such as diltiazem, low-dose dopamine (3 mcg/kg/min), and adequate hydration. Tacrolimus and cyclosporine are both associated with significant renal toxicity; therefore, administration of these agents is sometimes delayed to prevent further damage to the transplanted kidney with ATN. Stress ulcer prophylaxis may be indicated for many transplant patients. Two definite risk factors are mechanical ventilation and coagulopathy.

Hemodialysis is another potential risk factor for stress ulcer development. Most transplant patients have one or more risk factors for a stress ulcer. In addition, transplant patients receive large doses of corticosteroids and other medications that could precipitate or worsen gastritis. As a result of this increased risk, patients should receive pharmacologic stress ulcer prophylaxis immediately postoperatively.

Within the first 48 hours after transplantation, patients require intravenous opioids for pain control. However, as soon as the patient's pain begins to subside (within about 2 to 3 days), medication should be converted to oral dosage forms and administered on an as-needed (PRN) basis. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) for pain control is not recommended in this patient population, because combining them with either cyclosporine or tacrolimus may result in synergistic nephrotoxicity.

Perioperative Antibiotic Prophylaxis and Early Infectious Complications

Although surgery increases the risk of infection in many otherwise healthy individuals, infection poses even further risk for patients following organ transplantation. The need for immunosuppressives in addition to the pre-existing functional immunosuppression of end-stage renal and liver diseases places these patients at high risk for life-threatening infections. Within 3 months of transplant, infectious complications are common in both liver and kidney recipients, and may be associated with significant mortality rates. Largely because of differences in surgical techniques among transplant centers, the postoperative pathogens most commonly associated with infections differ. But in all centers, the high rate and severity of postoperative infectious complications solidifies the role of perioperative antibiotic prophylaxis for both liver and kidney transplantation.

Liver Transplantation

Liver transplantation represents one of the most technically difficult abdominal surgeries, with

procedure times lasting on average from 8 to 12 hours. Liver transplantation is classified according to the wound classification criteria of the Centers for Disease Control as a clean-contaminated procedure. Clean-contaminated procedures are defined as procedures that involve transection of gastrointestinal, oropharyngeal, genitourinary, biliary, or tracheobronchial tracts with minimal spillage or with minor breaks in technique.

Historically, liver transplant patients have received perioperative antibiotics, although strong placebo-comparative evidence for this practice does not exist. Despite this lack of evidence for use of perioperative antibiotics, clinicians recognize that the benefits of administering antibiotics seem to outweigh the risks. Appropriate perioperative antibiotics target potential bacterial infections from pathogens commonly associated with early (≤ 2 weeks after procedure) infections. The bacteria most commonly associated with intra-abdominal and wound infections (i.e., coagulase-negative *Staphylococcus aureus*, enterococci, and gram-negative bacilli, such as *Klebsiella*, *Escherichia coli*, *Enterobacter* spp. and *Citrobacter* spp.), originate from skin and intestinal lumen flora.

The most commonly used antimicrobial regimen is ampicillin plus cefotaxime. This regimen provides activity against common gram-negative pathogens, some antistaphylococcal activity, and activity against enterococcus. Studies have also examined the use of ampicillin/sulbactam and other third-generation cephalosporins. Other clinical trials have examined whether 48 hours of perioperative antibiotic prophylaxis is as effective as other longer duration regimens.

Selective bowel decontamination, another strategy to prevent post-transplantation infections, uses oral gentamicin, colistin (polymyxin E), and nystatin to clear the bowel of aerobic gram-negative bacilli and yeast. Since these agents are not well absorbed systemically, they serve to clear the gut of target organisms while avoiding systemic exposure of the drugs. However, this practice is controversial.

During the immediate post-transplant period in the ICU, the liver transplant patient can acquire nosocomial infections typical of that clinical setting. As in other postsurgical patients, these infections most commonly include ventilator-associated pneumonia, urinary tract infections (UTIs), infections associated with indwelling vascular access devices, surgical wound infections, and candidal superinfections. Initial empiric antimicrobial therapy should begin with broad-spectrum antibiotics, with shifts to antibiotics targeted to specific pathogens as culture and sensitivity results become available. Liver transplant patients may be more susceptible to candidal infections than are other postsurgical patient populations, due to surgical manipulation of the GI tract colonized with *Candida* spp. and because the amount of time they stay in the ICU increases their chances of nosocomial infections. Risk factors include elevated pre-transplant serum creatinine, hemodialysis, duration of ICU stay, antibiotic use (other than perioperative antibiotics), and immunosuppression. Both fluconazole and amphotericin B have been studied as candidal prophylactic agents. Several studies have shown a benefit with the use of fluconazole for antifungal prophylaxis in patients deemed to be at high risk. Amphotericin B is considered second-line therapy for this use because of its nephrotoxicity.

Kidney Transplantation

Infections within the first 2 weeks of kidney transplantation usually result from skin flora. Perioperative antibiotics are thus targeted toward *Staphylococcus aureus*, coagulase-negative staphylococci, and streptococci. Cefazolin is the most common agent used for antibiotic surgical prophylaxis in kidney graft recipients.

The most common infectious complication immediately after renal transplantation is UTI. Once symptoms appear, a urine culture should be obtained, and empiric antibiotics are directed toward the most common pathogens: *Escherichia coli*, other gram-negative rods, and *Staphylococcus aureus*. First-line therapy usually consists of

sulfamethoxazole–trimethoprim or ciprofloxacin, as the commonly isolated organisms are usually susceptible to these two agents.

Since kidney transplant patients do not usually have extended ICU stays or receive multiple antibiotic courses, they are less likely to acquire pulmonary infections and candidal superinfections.

SUBACUTE CARE

As noted previously, transplant patients vary in their time spent in the ICU. After kidney transplant, most patients spend less than 12 hours—if they are admitted to the ICU at all. But most liver transplant patients require an ICU stay of 1 to 3 days. In addition to continued monitoring of hemodynamics, respiratory status, fluid and electrolytes, other issues must also be addressed.

Acute Rejection

Rejection can present as several different types after transplant. Hyperacute rejection occurs within minutes to 24 hours after transplant and frequently results in graft loss. Fortunately, this is rare and is prevented with appropriate cross-matching between donor and recipient. Accelerated rejection occurs from 2 to 5 days post-operatively and is also rare. Chronic rejection, discussed later in this review, occurs months after transplant.

Most common type of rejection is acute rejection. Acute rejection presents most commonly one to three weeks postoperatively but up to 6 months after the transplant. Prevention is most important for long-term outcome. With the increased availability and use of new immunosuppressive agents, the incidence of acute rejection has decreased to less than 20% in kidney transplant recipients and to 30% to 50% in patients receiving liver transplants. Treatment of acute rejection necessitates the use of corticosteroids and/or antilymphocyte antibody therapy.

Clinical signs and symptoms of acute rejection are nonspecific, if they occur at all, in both kidney and

liver transplant patients. Symptoms may include fever, chills, myalgias, weight gain, edema, and pain and tenderness around the graft site. Kidney transplant recipients may have decreased urine output, along with hypertension. This must be distinguished from infection, calcineurin inhibitor toxicity, dehydration, and recurrence of disease. The most common presentation in kidney patients is an acute rise in serum creatinine; this is often the only indication clinicians receive of acute rejection. Because of the relative lack of generalized symptoms in many kidney transplant patients and the association between an episode of acute rejection and poorer outcomes (chronic rejection and ultimately graft loss), clinicians have sought more sensitive and specific markers that can either be determined in blood or urine and may detect rejection at a much earlier stage. These are called surrogate markers. Investigators are evaluating detection of markers such as C-reactive protein and serum amyloid (which are both phase reactants), cytokines (e.g., IL-10), and urinary proteins (e.g., perforin and granzyme B) in the setting of acute rejection. Specific patterns must distinguish acute rejection from infection and other types of renal injury (acute tubular necrosis, drug-induced nephrotoxicity and chronic rejection). Another approach that has been advocated by some investigators is the use of “protocol biopsy,” where a kidney transplant patient has a kidney biopsy performed on a regular basis (i.e., 1, 3, 6, and 12 months) whether or not there is a clinical indication. With this approach, some investigators have found that some patients have what is referred to as “subclinical” rejection and that this should be treated. This approach to patient care is currently being debated.

In addition to the nonspecific symptoms noted above in liver transplant recipients, ascites may occur or increase, and a decrease in the quantity and quality of bile may be present. The most likely indicators of acute rejection are elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase

(AP), and bilirubin. Infection and disease recurrence must be ruled out.

In the case of both kidney and liver transplant patients, tissue biopsy must be performed to confirm the diagnosis of acute rejection. This will dictate appropriate management.

Transitioning from Inpatient to Outpatient Settings

During the inpatient transplant period, several events are occurring simultaneously: fine tuning of immunosuppressive agents and other medications, reinstatement of treatment of pre-transplant comorbid conditions and medications, care of surgical wounds, and removal of catheters and drains. Also, focus is on the patient regaining strength; maintaining appropriate dietary intake, fluid intake, ambulation, and bowel function; and control of pain. These events are essential to ensuring adequate care by the patient and family after discharge.

Another important aspect that takes place is patient education and discharge planning. Many patients are discharged within 5 days after kidney transplant and 10 days after liver transplant. For positive long-term outcomes, patients must be educated about their medications; monitoring for and identification of problems; measuring and recording temperature, blood pressure, intake and output, and weight; and eating and exercising properly.

For the patient to make a smooth transition from inpatient to outpatient status, the inpatient pharmacist is instrumental. The pharmacist should be involved in patient education, helping to identify any issues that might make discharge and long-term care problematic. The pharmacist should communicate with transplant coordinators and make them aware of any outstanding issues. In addition, the hospital pharmacist should contact the community or clinic pharmacy from which the patient will obtain his or her medications after discharge. To assure continuity of pharmaceutical care, the community/clinic pharmacist should be in

contact with a member of the team, usually the transplant coordinator or hospital pharmacist involved with the care and discharge of the patient. Patients should leave the hospital with a good understanding of their condition and the names and contact information of the primary individuals responsible for their care. A list of current medications and a diary of important monitoring parameters that can be carried with them and made accessible to any health care provider involved in their care is important as well.

CHRONIC CARE

Although the most crucial time for a transplant recipient is during the initial hospital stay, many complications can occur after discharge from the hospital, and in fact, more grafts are lost to chronic rejection than acute episodes. Immunosuppressive regimens have been improved continually, with their greatest benefits being the reduction of acute rejection. Continued attention and vigilance are needed to identify, prevent, and treat immunologic and nonimmunologic long-term complications in transplant patients. All members of the health care team must be aware of common problems during long-term care, so that patients can have many years of health as a result of the successful transplant.

LONG-TERM IMMUNOSUPPRESSIVE STRATEGIES

Despite excellent short-term results, long-term graft failure and patient death are still major problems in kidney and liver transplantation. Graft failure in kidney transplant recipients is usually a function of cardiovascular disease or chronic rejection; in liver transplant recipients, graft loss and patient death are often related to recurrence of primary disease, renal failure, infections, or cardiovascular disease. For these reasons, long-term immunosuppressive strategies in kidney versus liver transplant patients differ greatly from short-term management.

In general, liver transplant recipients can tolerate a more rapid and pronounced withdrawal of

immunosuppression. This may include withdrawal of corticosteroids within 1 to 6 months and of antimetabolites within 6 to 12 months after transplant. Data is accumulating with regimens that avoid the use of corticosteroids altogether. Long-term liver transplant recipients often are receiving a calcineurin inhibitor as their sole immunosuppressant. Conversion protocols from a calcineurin inhibitor to agents such as sirolimus and mycophenolate are undergoing investigation.

On the other hand, kidney transplant recipients usually require a longer taper of their immunosuppression. Often they must be maintained on a two- or three-drug regimen. Each transplant center usually develops protocols that give guidelines on specific immunosuppressive use and withdrawal strategies. As with liver transplants, investigations with steroid avoidance, and conversion from calcineurin inhibitors are being conducted. Table 1 provides some general guidelines concerning long-term monitoring, adverse effects, and strategies for specific immunosuppressive agents.

Scheduled monitoring of transplant patients is a very important part of their care. Table 2 gives an example of a specific schedule. Some patients require more frequent and intense monitoring if they develop complications such as rejection, infection, or adverse drug events. Patients should continue to monitor their blood pressures, weights, intakes and outputs, temperatures, caloric intake, and when necessary, blood glucose values. This information is recorded in a patient diary for clinicians to review during routine clinic visits. Transplant recipients also must continue to monitor for potential danger signs and symptoms: fevers, nausea, vomiting, diarrhea, pain, decreased urinary output, rapid weight gain or loss, uncontrolled blood pressures, or uncontrolled blood glucose concentrations.

INFECTIONS

Infection is one of the most common life-threatening complications of long-term immunosuppressive

therapy. A patient's risk of developing infection is based on two factors: (1) the degree of exposure to given pathogens, and (2) the overall level of immunosuppression. Once a patient leaves the hospital, exposure to virulent pathogens is decreased and the risk of developing infections is lower. But many pathogenic bacteria, viruses, and fungi in the community can cause infections in immunosuppressed patients.

Etiology and Clinical Presentation

Transplant recipients are at highest risk for developing certain types of infections based on the amount of time that has passed since their transplant. In the first month post-transplant (while in the hospital and after discharge), the most commonly occurring infections include nosocomial bacterial and fungal infections of the surgical wound, lungs, urinary tract, and vascular access devices. These infections are not unlike those seen in nonimmunosuppressed surgical patients.

From 1 to 6 months after transplant, immunomodulating viruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) commonly recur in pre-exposed patients. CMV, a common and potentially serious viral infection in transplant recipients, is discussed in more detail below. Opportunistic infections caused by pathogens such as *Pneumocystis carinii*, *Aspergillus*, and *Listeria* become more prevalent. It is during this period that prophylactic antimicrobial use is critical to prevent these potentially fatal infections. Table 3 presents information on specific types of infections, causative pathogens, most common symptoms, suggested prophylactic regimens for prevention, and treatment options.

Once patients pass the sixth month post-transplant mark, their infection risks fall into three categories. More than 80% of patients have good graft function and are maintained on minimal amounts of immunosuppression. This group of patients has

similar infection problems to those of the general public, such as intestinal and respiratory viruses and community-acquired bacterial pneumonias. Opportunistic infections are rare in this group unless the transplant patient has been exposed to a particularly virulent pathogen.

The second group of transplant recipients (10%) goes on to develop chronic infections with certain viruses, such as CMV, EBV, HBV, or HCV. These viruses can cause serious morbidity, including serious organ damage. Long-term antiviral therapy is often used in these patients.

Patients in the final group (10%) develop recurrent acute rejections or chronic rejection, and they must take larger amounts of immunosuppressive agents as a result. Long-term immunosuppression leads to chronic viral infections and an increased risk for opportunistic infections, including *Pneumocystis carinii*, *Listeria*, *Nocardia*, *Cryptococcus*, and *Aspergillus*. Often, these patients require lifelong antibiotic and/or antifungal prophylaxis.

Cytomegalovirus Infection and Disease

CMV is the most common and most important post-transplant infection. A ubiquitous virus in the Herpes virus family, it often infects patients within 1 to 6 months after transplantation. Presence of the virus potentiates the risk of concomitant bacterial and fungal infections. CMV may also be associated with chronic injury to the transplanted organ.

CMV in transplant recipients usually originates from an antibody-seropositive donor organ, seropositive blood donors, or from reactivation of latent viruses secondary to immunosuppression. The CMV infection rate is 5% when both the organ donor and recipient are seronegative for antibodies to the virus. But when an antibody-positive donor organ is transplanted into an antibody-negative recipient, CMV infects 80% to 100% of organ recipients. However, the availability of effective prophylactic anti-viral agents, such as ganciclovir and valganciclovir, has significantly reduced the

frequency and severity of CMV infection and disease after transplantation. In addition to transplant of an organ from a seropositive donor into a seronegative recipient, other risk factors for development of CMV disease include advanced age (over 65), transfusion of large amounts of perioperative blood, and use of antilymphocyte antibodies or large amounts of immunosuppressive agents. Also, patients who require a retransplant because of acute rejection have a higher incidence of CMV disease. (see Table 3).

Diagnosis of CMV is based on both clinical and laboratory findings. Serological diagnosis is based on positive antibody seroconversion from a previously seronegative person (fourfold or greater increase in antibody titers). CMV may be detected by culturing body fluids, such as bronchoalveolar lavage, urine, blood, and tissue biopsy. Since CMV is contained within the host's white blood cells, large intranuclear inclusion bodies can be demonstrated using microscopy. However, identification of virus in the blood (antigenemia) or positive antibody seroconversion is not diagnostic for active disease, unless clinical signs and symptoms are present. Intravenous ganciclovir is the first-line agent used for the treatment of CMV disease in solid-organ transplant patients. Foscarnet is considered a second-line agent because of its severe adverse effects. Additionally, CMV hyperimmune globulin and nonspecific immunoglobulins have been used in combination with antiviral agents for refractory cases.

Prevention of CMV using antiviral prophylaxis is desirable. The ideal prophylactic regimen has not been determined. Most transplant centers have protocols specifying which patients should receive prophylaxis and which agents to use. Commonly used regimens include oral and intravenous ganciclovir, oral valganciclovir, oral acyclovir, and intravenous CMV hyperimmune globulin. Prophylaxis is usually continued for the first 3 to 4 months after transplant.

Because prophylactic therapy is expensive and not always effective, pre-emptive therapy has been used to prevent CMV disease. The technique involves withholding prophylactic therapy and monitoring laboratory tests to identify presymptomatic CMV viremia. CMV antigenemia may be the best predictor of clinical CMV disease, when compared with polymerase chain reaction (PCR) serology and shell viral assay. Once viremia develops, patients will usually require treatment with intravenous ganciclovir. However, opinions differ on which patients should receive preemptive therapy and when treatment should be initiated.

Other Viral Infections

In addition to CMV, a number of other viruses can also be transmitted from the donor or reactivated in the recipient. These include human herpes virus 6, 7, and 8 (HHV-6, HHV-7, HHV-8), adenovirus, polyoma (BK or JC) virus. The onset of occurrence may vary from the first few months as seen with HHV-6 to more than six months after transplant as in the case of polyomavirus. Some viruses, such as HHV-6 and HHV-7, are associated with coinfection with CMV. HHV-8 is associated with Kaposi's sarcoma. Polyomaviruses, of which BK, the most prevalent, has been implicated in the development of interstitial nephritis in 5% of renal transplant recipients. Forty-five percent of these patients develop graft failure; this infection often occurs within the first year. In the case of renal transplant patients who present with hematuria, urinary tract obstruction or slowly increasing serum creatinine, polyomavirus should be considered. There are no effective treatments and reduction of immunosuppression may be required. The impact of these viruses on the transplant recipient and their relationship to clinical disease continues to evolve.

OSTEOPOROSIS

Osteoporosis is a common condition among patients in general, owing to factors such as menopause in women, family history, small frame, smoking, alcohol and caffeine consumption, sedentary lifestyle, and inadequate calcium intake.

Among patients with organ transplants, however, the risk of osteoporosis is increased. Risk factors unique to transplant patients include their pre-transplant underlying disease state (such as end-stage kidney and liver disease) and use of bone-depleting immunosuppressant agents, such as corticosteroids, cyclosporine, and tacrolimus. The most critical period of bone loss appears to be the first 6 months after transplant.

Glucocorticoids inhibit calcium absorption from the gastrointestinal tract, induce urinary calcium loss, inhibit bone formation, and accelerate bone resorption. Cyclosporine and tacrolimus increase bone resorption, leading to bone loss. When a calcineurin inhibitor is used in combination with glucocorticoids, the effects on bone are more pronounced than when either agent is used alone. These effects are dependent on drug dose and duration of treatment. Therefore, early and rapid taper of immunosuppressive agents is an important strategy to help minimize bone loss during the first 3 to 6 months after transplant.

Pre-existing osteomalacia is almost always present in patients undergoing kidney and liver transplantation. In renal disease, this usually results from the kidney's inability to produce 1,25-dihydroxy-vitamin D₃. This, in turn, leads to hyperparathyroidism and bone loss. In liver disease, the bone loss is usually more pronounced because of factors such as altered vitamin D metabolism, malabsorption of calcium, alcoholism, poor nutrition, and hypogonadism.

All transplant patients should receive a thorough pre-transplant evaluation to determine their risk of developing osteoporosis. This should include a complete history to assess and minimize modifiable risk factors, dual-energy X-ray absorptiometry (DEXA) to assess bone density, and blood and urine laboratory tests to identify and correct metabolic and secondary causes of bone loss. In addition, these tests should be maintained after transplant (every 6 months for the first 18 months post-transplant and annually thereafter).

Table 4 lists more specific information about the prevention and management of osteoporosis in transplantation. Preventive therapy should be considered in every transplant patient. Once a transplant patient develops osteoporosis, effective treatment approaches are difficult to determine, as they are in the general population. Current treatment options include, but are not limited to, calcitonin, bisphosphonates, and hormonal replacement (HRT). Alendronate and risedronate are indicated for corticosteroid-induced osteoporosis. Agents such as raloxifene and fluoride are controversial. Calcium and vitamin D supplementation is recommended in all patients receiving corticosteroids as well as in osteopenic and osteoporotic transplant patients, as no treatment will work in the absence of adequate calcium and vitamin D.

DIABETES

Post-transplant diabetes mellitus (PTDM) is another complication. A growing body of evidence links hyperinsulinemia and hyperglycemia with an increased risk of developing atherosclerosis and cardiovascular disease. The leading cause of death among long-term transplant recipients—especially kidney transplant recipients—is cardiovascular disease. It is therefore extremely important to identify and effectively treat PTDM, otherwise its microvascular and macrovascular complications ensue more rapidly.

Currently, no consensus definition of PTDM has emerged. Some clinicians recommend looking solely at fasting blood glucose levels (FBGs) on three separate occasions; others advocate the use of oral glucose tolerance tests (OGTTs) in addition to FBGs, while still others suggest the additional use of serial glycosylated hemoglobin (HbA_{1c}) concentrations. One recently proposed definition is a blood glucose of >400 mg/dL at any one point, >200 mg/dL for more than 2 weeks, or the need for insulin treatment for at least 2 weeks. This, along with the use of serial measurements of HbA_{1c} should form the basis for diagnosing PTDM. Based on

the varying methods of defining and identifying PTDM, the incidence has been reported to be 4% to 20%.

Recognition, prevention, and treatment of PTDM is a very important aspect of a transplant recipient's long-term care plan. Every transplant patient must be prescreened for potential risk factors for developing PTDM. These include impaired OGTT, impaired C-peptide secretion, and African-American or Saudi-Arabian ethnicity. Additionally, any patients who have risk factors for developing type 2 diabetes mellitus are at higher risk for developing PTDM (e.g., advanced age, obesity, sedentary lifestyle, family history of diabetes, hypertension).

Some of the immunosuppressive agents used in transplantation increase the risk of developing PTDM. Corticosteroids likely decrease the number and affinity of insulin receptors, impair glucose uptake in the musculature, impair insulin production, and impede the activation of the glucose/free fatty acid cycle. Corticosteroids also induce insulin resistance. Cyclosporine and tacrolimus may inhibit specific cellular proteins, resulting in the decreased production of insulin from beta cells in the pancreas. This effect appears to be dose-dependent. Although initially this may be reversible, long-term use of cyclosporine or tacrolimus may cause irreversible damage to the beta cells of the pancreas.

Experts differ as to which of these agents is more diabetogenic. The increased potency of tacrolimus may induce a more pronounced impairment of insulin production and secretion, compared with cyclosporine. However, this may be offset by steroid-sparing effects of tacrolimus-based immunosuppressant regimens. Sirolimus or mycophenolate mofetil are not associated with development of PTDM.

Since calcineurin inhibitor and corticosteroid dose and duration are important factors associated with

PTDM, most prevention strategies center around reducing or altering immunosuppressant regimens in at-risk patients. Usually, rapid tapering of corticosteroids is suggested. The ultimate goal in this strategy is early discontinuation of the corticosteroid. Unfortunately, this may not be possible in patients who have or are at high risk for having acute cellular rejection. By using one of the newer immunosuppressants, such as mycophenolate mofetil or sirolimus, it may be feasible to discontinue or to reduce the dose of the diabetogenic immunosuppressants. Although these newer agents are not directly associated with PTDM, dose-dependent hematologic adverse effects (i.e., thrombocytopenia, leukopenia, neutropenia) have been noted, and in addition, cardiovascular adverse effects (i.e., hypercholesterolemia, hypertriglyceridemia, hypertension) frequently occur with sirolimus. Regardless, if a patient is known to have, or is at high risk for developing PTDM, monitoring of blood glucose and HbA_{1c} values, and urine protein excretion is warranted. Patients should be educated about other known risk factors, such as hypertension, smoking, dyslipidemia, and obesity, and appropriate modifications and interventions should be encouraged.

The treatment of PTDM is similar to the treatment of type 2 diabetes mellitus, with certain exceptions. Although some patients can be controlled on oral agents, most patients will require exogenous insulin. In theory, agents such as metformin, rosiglitazone, and pioglitazone would be beneficial in this population because of their postulated mechanisms of action. However, extreme caution should be used when initiating any of these agents based on their relative contraindications (renal dysfunction) and potential side effects (hepatotoxicity). Hypoglycemic therapy can often be discontinued once a patient's immunosuppressive regimen is altered or reduced, so patients should be monitored for this possibility.

A patient with PTDM should be educated on the same issues as a diabetes mellitus patient,

including proper serum glucose monitoring, warning signs of hyperglycemia and hypoglycemia, diet, foot and eye care, and cardiovascular risk reductions.

MALIGNANCY

Although malignancies following transplantation are rare, a transplant patient is 20 to 50 times more likely to develop a malignancy than other patients. The most common types of cancers in this population are squamous cell carcinomas of the skin, non-Hodgkin's lymphomas (NHL) commonly termed post-transplant lymphoproliferative disorder (PTLD), Kaposi's sarcoma, *in situ* carcinomas of the uterine cervix, carcinomas of the vulva and perineum, hepatobiliary carcinomas, and a variety of sarcomas. The overall incidence of cancer is approximately 6% in this population, and the average age at diagnosis is only 42 years.

Since the two most common types of tumors in transplant recipients are cancers of the skin and lips and non-Hodgkin's lymphoma, the scope of this discussion will be limited to these two cancers.

Skin and lip cancers account for roughly 37% of all cancers seen in transplant recipients. Depending on sun exposure, its incidence is 7 to 21 times higher among transplant patients, compared with the general population. This risk increases with time after transplant, with up to a 54% incidence at 20 years after transplant. Unfortunately, when these cancers develop in transplant patients, they are usually more aggressive and metastasize earlier. This is why it is extremely important to counsel transplant recipients on the avoidance of sun exposure and the copious use of sunscreens and protective clothing (brimmed hats or sun visors). This is especially true in individuals who may be at higher risk because of their characteristic traits (blond or red hair, fair skin, and blue eyes).

All transplant patients should be examined on a regular basis for identification and removal of any premalignant skin lesions. Treatment options for skin cancers include surgical excision, topical 5-fluorouracil, cryosurgery, or radiotherapy.

The second most common cancer experienced by transplant recipients (PTLD). Reported to occur in up to 5% of transplant patients, its incidence varies greatly. Risks of PTLT increased by 28-fold to 49-fold have been observed, compared with the general population.

PTLD is a morphologically diverse cancer. It can occur anywhere from one to more than 10 years after transplant. Polyclonal hyperplasia usually appears within the first year of transplantation.

Patients with PTLT may present with fever, pharyngitis, and adenopathy. PTLT that presents early after transplant (within the first year) is usually less aggressive and responds well to reductions in immunosuppression. Conversely, late-presenting PTLT often is difficult to treat and does not usually respond well to reductions in immunosuppression. A major risk factor for developing PTLT is the degree of immunosuppression. Additionally, pediatric patients who are EBV-antibody negative at the time of transplantation have a substantially higher incidence of PTLT. Thus, the usual cause of primary infection in the pediatric patient is an EBV positive graft from an EBV positive donor to an EBV negative recipient. Presence of EBV and development of PTLT are closely associated. The development of PTLT from EBV infection follows a stepwise process, beginning with a primary infection of B cells by EBV. This progresses into a latent infection. Reactivation of EBV occurs in transplant patients receiving long-term immunosuppression. This eventually leads to malignant B cells developing by mechanisms that are not fully understood.

Management of PTLT, often very difficult, is complicated by late diagnosis of the disease and poor performance status of patients at the time of diagnosis. Initially, reduction in the degree of immunosuppression is attempted. This often produces a good response in patients with less aggressive forms of PTLT. But this condition almost universally responds poorly to chemotherapy. Radiotherapy may increase survival rates in

patients with localized disease. Monoclonal antibodies, such as rituximab, have shown promising results.

CHRONIC REJECTION

Kidney Transplants

Chronic rejection remains the most common cause of graft loss in renal transplantation. Although the incidence of acute rejection episodes dropped significantly during the 1990s, the incidence of chronic rejection remained largely unchanged, accounting for approximately 15% to 20% of all graft failures.

Most classifications of chronic rejection are based on tissue biopsy results, including interstitial fibrosis and tubular atrophy. But the definition of chronic rejection is not universally consistent, and other classification schemes require the presence of atherosclerosis in the renal vasculature.

Chronic rejection is evidenced 6 months after the transplant, but it is more likely to occur 5 to 10 years after placement of the graft. Clinical manifestations of chronic rejection include a steady progressive worsening of renal function, as indicated by increasing serum creatinine concentrations, proteinuria, and arterial hypertension. Urinary protein excretion of 1 to 2 grams per day is highly suggestive of chronic rejection. Early diagnosis is a key to prevention. Diagnosis based on tissue biopsy also helps differentiate between chronic rejection and other problems that may present with the same clinical and laboratory findings, such as acute cellular rejection or calcineurin inhibitor nephrotoxicity.

Many immunologic and nonimmunologic factors have been implicated in increasing the likelihood of developing chronic rejection. Nonimmunologic factors include race, sex, size and match, hypertension, hyperlipidemia, and infection. African-Americans have a higher incidence of graft failure caused by chronic rejection. Interestingly,

recipients of organs from non-White male donors have inferior graft survival rates. Hyperlipidemia has been correlated to proteinuria, hypoalbuminemia, and chronic rejection. The fact that certain immunosuppressive agents cause dyslipidemias increases the importance of the recognition and proper treatment of this disorder.

Infection with CMV also has been associated with the development of chronic rejection. The most important immunologic factor implicated in the development of chronic rejection is the number of episodes and severity of acute cellular rejection.

Therefore, the monitoring and treatment of acute rejection is an important preventive measure to reduce the incidence of chronic rejection. Histo-incompatibility, insufficient immunosuppression, and the presence of HLA antibodies may also play a role in the development of chronic rejection.

Pharmacologic intervention has been largely unsuccessful in preventing chronic rejection. Strategies that have been attempted include the use of induction therapy with antilymphocyte antibodies; different and varying degrees of immunosuppressant regimens using cyclosporine, tacrolimus, mycophenolate mofetil, sirolimus, and leflunomide; control of blood pressure and lipids; and dietary supplementation with fish oils. Used to control blood pressure, angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers may be of some benefit in slowing the progression of chronic rejection. The use of statins to control lipids has gained much recognition recently and may also be of some use for reducing the progression of chronic rejection.

Liver Transplants

Chronic rejection in liver transplantation occurs in fewer than 5% of recipients. The reasons for this

are largely unclear, but a number of hypotheses include the fact that the liver has a large parenchymal cell mass, a large number of passenger leukocytes, low numbers of major histocompatibility antigen class I and II cells, and a regenerative capability. The liver is basically an immunologic organ capable of producing its own leukocytes, so its graft-versus-host response may be self-limiting and may in fact induce tolerance between the transplanted liver and the host's immune system. In fact, studies have shown that complete removal of immunosuppression can be tolerated in a small number of liver transplant recipients without detrimental consequences.

Chronic rejection in liver transplantation can occur early (3 to 6 months after transplant) but is more common 12 months or later after transplant. Clinically, chronic rejection usually presents as a moderately slow progressive increase in liver function tests (transaminases and bilirubin), coupled with a decline in the liver's synthetic function capabilities (coagulopathies, portal hypertension, and ascites). Late stages of chronic rejection may lead to arterial thrombosis.

If chronic rejection occurs, it must be diagnosed in similar fashion as in renal transplant patients. A transplant liver tissue biopsy must be performed for definitive diagnosis. On the tissue biopsy, chronic rejection is diagnosed by the absence of bile ducts in the portal triad.

Several studies have shown that conversion from cyclosporine to tacrolimus might be of some benefit in reversing or halting the progression of chronic liver rejection.

RECURRENCE OF DISEASE

Because of the increase in graft and patient survival accomplished in recent years, the recurrence of pre-transplant diseases is an important concern. Strategies should be developed for early diagnosis and prevention of recurrences in both renal and hepatic transplant recipients.

Recurrence of disease in renal transplant recipients includes various forms of glomerulonephritis, diabetes, amyloidosis, oxalosis, cystinosis, and sickle cell anemia.

In liver transplant recipients, those transplanted because of viral hepatitis (currently the leading reason for transplantation) are especially at risk. Recurrence of HBV in transplant patients has been substantially reduced with the use of antiviral agents, such as lamivudine, used in combination with long-term passive immunization with hepatitis B immune globulin.

But recurrence of HCV in post-transplant patients remains universal. These patients often are receiving lower amounts of immunosuppression in an effort to prevent unchecked viral replication. Additionally, studies are currently underway looking at the utility of interferon, ribavirin, and pegylated interferon in the post-transplant HCV-positive patient. Nonetheless, HCV recurrence—and subsequent end-stage liver failure and death—remains a major complication.

Other diseases that often recur in liver transplantation include autoimmune hepatitis, diseases of the biliary tree, and hepatocellular carcinoma.

IMMUNIZATIONS

Although immunization is an important part of infectious disease prevention in the general population, its role in transplant patients has not been well studied. Certainly, all patients awaiting transplant should have their immunizations brought up to date. These include diphtheria, tetanus, pertussis, and mumps–measles–rubella. Infants should receive Haemophilus influenzae type b vaccination. Additionally, the use of the hepatitis B, pneumococcal, and influenza vaccinations is generally recommended in patients awaiting transplantation. The use of varicella zoster virus vaccination in pre-transplant pediatric patients is also recommended.

Clinicians recommend using immunizations after transplant as long as the vaccine does not contain live viruses. A few small studies have shown the effectiveness of diphtheria, tetanus, H. influenzae, and inactive polio vaccines in post-transplant patients. Influenza also appears to be effective in the post-transplant patient, although response rates are less compared with immunocompetent people. Hepatitis B vaccine produces lower rates of antibody response in transplant patients, so pre-transplant administration of this vaccine series should be stressed. Pneumococcal infections are fairly common post-transplant, so booster vaccinations are recommended. To date, no vaccination study conducted in transplant patients has shown an increase in rejection rates or any other serious side effects, so use of preventive vaccination in the post-transplant population should be advocated.

DRUG INTERACTIONS

Pharmacists play a vital role in providing pharmaceutical care to transplant recipients through the recognition and prevention of potential serious drug interactions. Three of the major immunosuppressants currently prescribed—cyclosporine, tacrolimus, and sirolimus—are primarily metabolized and eliminated via the cytochrome P450 3A4 enzyme system, placing the patient at high risk for numerous drug interactions. Before any new drug is prescribed to these patients, its effect on metabolism of the immunosuppressants and other concomitant medications must be analyzed.

Use of drugs that inhibit or induce the cytochrome P450 3A4 system is not absolutely contraindicated, as this would eliminate a large number of important therapeutic options in these patients. One must be diligent in monitoring for organ function and adverse effects when adding or discontinuing an interacting agent. (see Table 5).

NONPRESCRIPTION MEDICATIONS AND DIETARY SUPPLEMENTS

Potential severe consequences may arise with the use of certain over-the-counter (OTC) medications in transplant recipients. It is important to educate and monitor these patients closely for nonprescription medication use. In addition to potential drug interactions through the cytochrome P450 3A4 enzyme system, nonprescription medications can often combine with the immunosuppressants to increase the likelihood of developing severe adverse drug reactions, including nephrotoxicity. This includes the use of very common classes of OTCs, such as NSAIDs, cough and cold products, herbal products such as St. John's Wort, and vitamins. Table 6 lists some of the more common reasons why people seek OTC medications, the nonprescription medications that should be avoided, and recommended alternatives for transplant patients.

With the recent explosion in the use of herbal products has come the increased identification of important herb–drug interactions. These interactions can be of a pharmacokinetic or pharmacodynamic nature. This is a difficult problem to address for a number of reasons. First and most importantly, the experimental data concerning drug–herb interactions are sparse. Little evidence is available from clinical trials, case reports, or case series reviews. To compound this issue, herbs are unregulated products that can be obtained from a plethora of sources. Additionally, patients often consider herbal products not to be drugs eliciting a pharmaceutical response, but rather as a supplement similar to vitamins. This leads to the under-reporting of herbal use during patient medication histories. Pharmacists and other health care professionals must, therefore, review each patient's medication profile carefully to identify potential drug–herb interactions and prevent any adverse consequences from them.

St. John's Wort has recently been identified to induce hepatic enzymes, and transplant recipients

taking this herb have had significant reductions in cyclosporine concentrations, resulting in rejection. The immunostimulating effects of Echinacea, Astragalus, licorice, alfalfa sprouts, and zinc may offset the immunosuppressive effects of the calcineurin inhibitors, antimetabolites, and corticosteroids. Feverfew, garlic, ginger, and ginkgo all increase the risk of bleeding. Additionally, ginseng should be avoided, as it may increase bleeding and augment the effects of corticosteroids. Guar gum may inhibit or slow the absorption of many agents, including the immunosuppressants. Saiboku-to may increase corticosteroid effects, while sho-salko (both Asian herb mixtures) may have the reverse effect. The use of chili pepper may increase the likelihood of developing ulcers in transplant patients.

Thus, in general, herbs should be avoided in this population. If a transplant recipient is adamant about taking herbal products, close therapeutic monitoring is required to ensure rapid identification and correction of drug–herb interactions.

MEDICATION NONADHERENCE

Another potentially dangerous problem in transplant patients is medication nonadherence. Identifying transplant patients with medication nonadherence difficulties is an important part of their long-term management, as drugs have been a major factor in improving outcomes in transplantation medicine over the past half century.

When a transplant recipient is not adhering to prescribed regimens, the health care team must identify and alleviate the secondary causes. Commonly encountered problems include medication cost, complexity of regimen, undesirable side effects, lack of proper education, and patient apathy or psychological difficulties. All of these problems can and must be overcome to help prevent patients from developing major complications, including graft loss and death.

DEVELOPMENT OF A PATIENT CARE PLAN

To provide optimal and efficient nursing, medical, or pharmaceutical care to transplant patients, the development of well-designed care plans is crucial. A formalized pharmaceutical care plan should provide a logical, consistent framework that identifies transplant recipients' drug-related problems, develops interventions to resolve or prevent the problems, documents the findings, and measures progress toward desired pharmacotherapeutic outcomes. Although the basic purpose of the pharmaceutical care plan is universal, the specific development of a patient care plan should be based on the most commonly encountered drug-related problems seen in a particular patient population. Each pharmacist must develop an outline for the care plan with which he or she is comfortable. To provide optimal pharmaceutical care, the pharmacist should be in close contact with all other health providers caring for transplant recipients, especially the transplant coordinator who is usually responsible for much of the important therapeutic decision making.

Steps to be taken include: Data Collection, Development of a Drug-Related Problem List, Assessment and Plan, Follow up and Documentation of Outcomes, and Payment for Professional Services.

STEP 1: DATA COLLECTION

Data collection is a vital part of the patient care plan and provides the information from which drug-related problems are exposed and corrected. Early post-transplant, patients have frequent and intense monitoring of their vital signs and laboratory values. Much of the therapeutic decision making is based on accurate collection and assessment of these monitoring parameters. As such, before any drug-related issues are addressed, it is important not only to closely review that particular day's monitoring parameters, but to review past values

as well. This will help identify trends in values that may give a better picture of what drug-related problems exist.

STEP 2: DEVELOPMENT OF A DRUG-RELATED PROBLEM LIST

Once all of the data collection has been completed accurately, a drug-related problem list is developed. This is similar to the differential list of problems a physician may develop, but is specific to drug-related issues. Often it is difficult to simply focus only on drug-related problems in the transplant population because certain diseases may actually cause similar effects as drugs. A problem list should consist of the observations made while reviewing trends in monitoring parameters and should focus on drug-related problems. All drug-related concerns on the problem list must be addressed, not just those related to immunosuppression.

STEP 3: ASSESSMENT AND PLAN

The assessment and plan are based on the accurate interpretation of the data collection, medications, and the problem list. Although using monitoring sheets can help streamline the data collection process, the analysis of these data by the pharmacist is based on an individual's therapeutic knowledge base and experience.

The plan should contain the recommended medication changes and future monitoring parameters to ensure appropriate pharmaceutical care. It should be as specific as possible, including new drugs, doses, frequencies, and routes. Monitoring recommendations should include which specific parameters are needed, such as laboratory values, frequency of desired monitoring, and any adjustments that may be necessary based on the results of the recommended parameters. The plan should focus on the best way to resolve or prevent any identified drug-related problems that were mentioned in the assessment.

STEP 4: FOLLOW UP AND DOCUMENTATION OF OUTCOMES

As the health care system continues to strive for efficient, cost-containing medical care, health care providers must demonstrate an ability to contribute significantly to developing better outcomes at reduced costs. In pharmaceutical care, this is achieved through documentation of complete pharmaceutical care plans, well-maintained notes, and appropriate follow up for necessary drug interventions.

STEP 5: PAYMENT FOR PROFESSIONAL SERVICES

Pharmacists continue to be recognized as important providers of health care, particularly on the state and local level with Medicaid and some third-party payers. This recognition has occurred in the form of changes in pharmacy practice acts in many states, recruitment of and contracting with pharmacists into physician practice groups, and Medicaid programs that pay pharmacists for the care of patients with conditions such as diabetes, asthma, dyslipidemia, and hypertension. Pharmacists have also been successful in establishing and obtaining payment for influenza and other vaccinations.

Despite this progress, many payers and other participants in various health care delivery systems (physicians and patients) are unaware of the services that pharmacists can provide. Even on the national level, pharmacists are not yet officially recognized as "providers." A number of national organizations are attempting to change this situation. Therefore, pharmacists who seek reimbursement must have specific plans and goals that can be communicated to payers, health care providers, and patients, and must be prepared to document improved patient outcomes resulting from their efforts.

In a hospital setting, the pharmacist would also have to be recognized as a provider. Usually this consists of applying for credentialing and hospital privileges. The pharmacist would have to submit the appropriate application form, evidence of licensure and liability insurance, a letter of support from one or more physicians, and a list of specific activities and location(s) of where services will be provided (i.e., outpatient clinic, inpatient consults).

Another important step is to develop a data collection and documentation system as illustrated in the previous section. This should include reason for patient encounter and intervention (subjective and objective information), intensity of evaluation (assessment), services provided (plan, follow up, and outcome) and patient contact time.

In summary, reimbursement for pharmacy services is possible, but it requires an understanding of rules and regulations governing provision and documentation of these services. Keep in mind that these can change and can be interpreted differently by local administrators for each payer. The pharmacist should contact the appropriate payers, particularly Medicare, and determine what is needed to become a provider, the proper procedures for submitting a claim, the circumstances and setting (hospital vs. freestanding pharmacy or clinic) required for the submission of claims, and the types of claims that can be submitted. The success a pharmacist achieves with this process is not based on how much compensation is received, but rather on the improvement in patient outcomes and the recognition that pharmacists play a vital role in the care of these patients.

Table 1
Long-term Immunosuppression Strategies

Drug Class	Usual Initial Dose	Long-term Dosing Strategies	Therapeutic Drug Monitoring	Common Long-term Adverse Reactions	Strategies to Prevent or Treat Adverse Effects
Cyclosporine <i>Calcineurin inhibitor</i>	6–10 mg/kg/day Q 12 hr, dose to maintain blood concentrations within therapeutic range	Slowly ↓ dose, usual long-term maintenance dose is 3–4 mg/kg/day Q 12 hr, dose to maintain blood concentrations within therapeutic range.	<1 mo: 250–350 ng/mL 1–3 mos: 150–200 ng/mL >3 mos: 50–150 ng/mL	Nephrotoxicity, HTN, Neurotoxicity, ↑blood sugars, ↑K, ↓Mg, ↑cholesterol/lipids, gingival hyperplasia, hirsutism, neoplasm	Maintain therapeutic drug concentrations, consider ↓ dose or changing to tacrolimus, monitor electrolytes, blood pressure and blood sugars, may need antihyperglycemic, antihypertensive, or lipid lowering (statin) therapy
Tacrolimus <i>Calcineurin inhibitor</i>	0.1–0.2 mg/kg per day Q 12 hr, dose to maintain blood concentrations within therapeutic range	Slowly decrease dose, usual long-term maintenance dose is 0.05–0.1 mg/kg/day dosed Q 12 hr. Dose to maintain blood concentrations within therapeutic range.	<1 mo: 10–20 ng/mL 1–3 mos: 10–15 ng/mL >3 mos: 5–10 ng/mL	Nephrotoxicity, HTN, Neurotoxicity, ↑blood sugars, ↑K, ↓Mg, neoplasm	Maintain therapeutic drug concentrations, consider ↓ dose or changing to cyclosporine, monitor electrolytes, blood pressure and blood sugars, may need antihyperglycemic, or antihypertensive therapy
Mycophenolate Mofetil <i>Antimetabolite</i>	1–3 g/day divided into BID–TID dosing	Taper and discontinue after 6–12 months post-transplant if patient is rejection free	Therapeutic range poorly defined and drug concentrations not routinely obtained	GI toxicities including bloating, cramping, diarrhea, N/V, and gastritis. Leukopenia, anemia, and thrombocytopenia	For GI toxicities, either ↓ the total daily dose or give same total daily dose more frequently. For severe heme toxicities, consider ↓ the dose or switching to another agent (sirolimus)
Azathioprine <i>Antimetabolite</i>	3–5 mg/kg/day dosed QD	Taper to 0.5–2 mg/kg/day and eventually discontinue if patient is rejection free in 6–12 months	Not routinely used in clinical setting	N/V, gastritis, leukopenia, thrombocytopenia, anemia, pancreatitis, and neoplasm	Consider ↓ the dose for minor toxicities and holding the dose for severe toxicities
Sirolimus <i>mTOR inhibitor</i>	6–15 mg loading dose, then 2–5 mg QD, may consider dosing to maintain blood concentrations within therapeutic range	Long-term maintenance strategies not well-developed, may consider using as sole long-term immunosuppressant or tapering off in 6–12 months if patient is rejection free	<1 mo: 5–15 ng/mL 1–3 mos: 5–10 ng/mL >3 mos: 5–10 ng/mL	Hypertriglyceridemia, hypercholesterolemia, thrombocytopenia, pneumonitis, impaired wound healing	Decrease the dose or change to another agent. Monitor lipids closely, many patients need lipid lowering therapy (statins or fibrates).
Corticosteroids <i>Steroid</i>	Varies between transplant centers. Usually start with 500–1000 mg IV methylprednisolone for 1–3 days, then taper rapidly to 15–20 mg PO prednisone over 7–14 days.	Taper slowly to eventually 5–10 mg prednisone QD, then discontinue if patient is rejection free at 6–12 months and at low-risk of having rejection	Not routinely used in clinical setting	Weight gain, fat redistribution (buffalo hump), osteoporosis, glucose intolerance, cataracts/glaucoma, HTN, gastritis, ulcers, N/V, acne, personality changes, adrenal suppression	Decrease dose and taper off as quickly as tolerated. Monitor blood sugars, blood pressures, weight, lipids, eye exams, and bone scans. May need pharmacological treatment for hyperglycemia, hypertension, gastritis, adrenal suppression, and osteoporosis with long-term steroid use.

Table 2
Suggested Transplant Recipient's Monitoring Schedule

Postoperative Time Interval	Laboratory Blood Draws	Clinic Visits
0–2 weeks	Three times per week	Once weekly
2–4 weeks	Two times per week	Every other week
1–3 months	Once weekly	Every 2–4 weeks
3–6 months	Every other week	Once monthly
6–12 months	Once monthly	Every 1–2 months
> 12 months	Once monthly	Every 3–6 months

Table 4
Prevention and Treatment Strategies for Osteoporosis in Transplant Recipients

Prevention Strategies	Treatment Strategies
<p>Diagnose and treat any underlying disorders that adversely affect bone and mineral metabolism</p> <p>Reduce calcineurin inhibitor doses as quickly as possible</p> <p>Use lowest possible doses of corticosteroids (7.5 mg or less of maintenance prednisone doses)</p> <p>Maintain regular weight-bearing exercise program</p> <p>Dietary elemental calcium consumption of 1000 mg for men and premenopausal women; 1500 mg for postmenopausal women</p> <p>Intake of 400–800 IU of vitamin D daily</p> <p>Discontinue or reduce use of alcohol, tobacco, and caffeine</p> <p>Avoid use of loop diuretics and replace with hydrochlorothiazide if possible</p> <p>Begin hormone replacement therapy in postmenopausal women if not contraindicated</p> <p>Monitor and replace testosterone in men with hypogonadism</p>	<p>Calcitonin 200 IU intranasally qd (alternate nostrils) – may decrease bone pain as well (within 14 days of initiating therapy)</p> <p>Etidronate 400 mg PO qd for 14 days, given every 3 months</p> <p>Alendronate 5–10 mg PO qd</p> <p>Men – if testosterone serum concentration is low – 100 mg testosterone enanthate or cypionate IM q 14 days OR testosterone 5 or 6 mg patch applied qd</p> <p>Women – postmenopausal- conjugated estrogen with progesterone 0.625/2.5 mg PO qd OR raloxifene 60 mg PO qd if estrogen contraindicated</p> <p><i>ALL Osteoporotic patients should receive 1500 mg of elemental calcium and 800 IU vitamin D daily</i></p>

Table 3
Common Post-Transplant Opportunistic Infections

Pathogen/ Disease	Symptoms of Clinical Disease	Clinical Manifestations	Usual Time of Onset	Recommended Prophylaxis	Treatment Options	Comments
Cytomegalovirus CMV	Fever, chills, N/V, diarrhea, cramping, ↓ WBC, ↓ platelets, and (+)CMV antigenemia or PCR. If end-organ damage, changes in SCr, AST, ALT, Tbili, and PFTs.	Range from asymptomatic CMV syndrome to end-organ damage; Can affect GI tract, liver, kidneys, CNS and lungs. High mortality with end-organ damage.	1 to 6 months post-transplant. In patients receiving antiviral prophylaxis (especially D+/R-) onset may be delayed until after withdrawal of prophylaxis.	First-line: ganciclovir ^a 1000 mg PO TID w/ meals for 3–4 mos. Second-line: acyclovir ^a 200–800 mg PO TID or CMV hyperimmune globulin 100–150 mg/kg IV q2 wks for 12 wks (6 doses).	First-line: ganciclovir ^a 5 mg/kg/dose IV BID for 14–21 days, then 1000 mg PO TID for 4 wks. Second-line: foscarnet ^a 60–90 mg/kg/dose q8–12h for 14–21 days.	During treatment monitor for signs of improvement: ↓ fevers, ↑ WBC, ↑ platelets, (–) CMV antigenemia. Ganciclovir may cause ↓ WBC, ↓ platelets, neurotoxicity.
Pneumocystis carinii PCP	Dyspnea, fevers, non-productive cough, tachypnea, tachycardia, cyanosis, and chest x-ray changes.	Remains confined to lungs, rarely causing disseminated disease. If left untreated, progressive respiratory distress leading to death.	Usually occurs between one and 12 months post-transplant. May occur later if patient is receiving large amounts of long-term immunosuppression.	First-line: TMP/SMZ ^a 1 SS or DS tab PO q MW for 6–12 months. Second-line: Pentamidine 300 mg inhaled once monthly or dapsone 50 mg PO qd.	First-line: TMP/SMZ ^a 10–20 mg/kg/d divided BID–QID x21 days. May switch or use PO in resolving or mild cases. Second-line: Pentamidine 4 mg/kg IV QD x21 days.	Disease rarely occurs in transplant recipients receiving adequate prophylaxis.
<i>Candida albicans</i> Thrush	Discrete and confluent adherent white plaques on oral and pharyngeal mucosa. Plaques are usually painless.	May lead to esophageal candidiasis causing dysphagia and substernal pain. If untreated, may also lead to severe disseminated disease.	Varies greatly. Usually occurs early (<1 month) post-transplant. However, may occur at anytime in patients receiving course of broad-spectrum antibiotic.	First-line: nystatin suspension 5–10 mL swish and swallow TID after meals for 2–4 weeks post-transplant, then each time receiving antibiotic course. Second-line: fluconazole ^a 100 mg PO qd.	First-line: nystatin suspension 5–10 mL swish and swallow TID after meals. Second-line: fluconazole ^a 100 to 200 mg PO qd.	Fluconazole-resistant <i>Candida albicans</i> now seen more frequently in transplant patients. Non- <i>albicans Candida</i> species (<i>C. tropicalis</i> , <i>C. parapsilosis</i> , <i>C. glabrata</i> , and <i>C. krusei</i>) becoming more prevalent
Enterobacteriaceae, fungi UTIs	Fever, dysuria, polyuria, ↑ WBC, positive urinalysis, and positive urine culture.	Ranges from simple non-complicated UTI to pyelonephritis and urosepsis in untreated patients.	Usually occurs early post-transplant (<1 month). May occur later in patients on large amounts of immunosuppression, or in patients with ureteral stents, urinary reflux, or urinary retention.	First-line: Use of TMP/SMZ ^a in prevention of PCP also may prevent UTIs. Other antibiotic prophylaxis not routinely used unless patient at high-risk for developing chronic UTIs.	Treatment should be based on cultures and sensitivities. Avoid antibiotics that may have similar toxicities to the immunosuppressants (such as aminoglycosides ^a).	

^aThese agents require adjustment for renal dysfunction

Table 5
Potential Drug Interactions with Immunosuppressant Agents

Immunosuppressant	Interacting Agent(s)	Mechanism	Significance	Management
Corticosteroids	Phenytoin, phenobarbital, rifampin	Cytochrome P450 3A4 enzyme inducers	Increases hepatic metabolism of steroids, decreases absorption	Higher doses of corticosteroids may be required, monitor patient
	Oral contraceptives		Increase serum concentrations	May need to decrease dose of corticosteroid
	Cyclosporine		Increases half-life	Need to decrease dose of corticosteroid
	Salicylic Acid		Decreases clearance of methylprednisolone	Decrease dose or increase interval of corticosteroid
	Metronidazole		Corticosteroids increases excretion of metronidazole	Higher doses may be required to treat infections adequately
	Pancuronium		Prednisone increases elimination of pancuronium, rapidly reverses neuromuscular blockade (NMB)	Monitor and make dose adjustments, best to use other NMB agent
Azathioprine	Allopurinol	Inhibits the metabolism of azathioprine		
	Pancuronium		Azathioprine inhibits pancuronium's actions	
	Succinylcholine		Azathioprine potentiates succinylcholine's actions	
	Warfarin		Decreased warfarin effect when used with azathioprine	
	Sulfonamides, ganciclovir, cyclophosphamide, methotrexate, ACE inhibitors, mycophenolate mofetil	Similar toxicity profiles between agents	Enhanced bone marrow toxicity	Monitor for toxicity and adjust doses accordingly, do not use azathioprine and mycophenolate mofetil in combination
	Cholestyramine, metronidazole	Disrupt enterohepatic circulation	Decreases mycophenolate mofetil serum concentrations	Need to monitor closely, and possibly increase mycophenolate mofetil dose
	Antacids	Decreases mycophenolate mofetil absorption	Decreases mycophenolate mofetil serum concentrations	Possibly increase mycophenolate mofetil dose
Mycophenolate Mofetil	Acylovir and ganciclovir	Potentially compete for renal tubular secretion	May increase concentrations of either agent	Conflicting data on extent of interaction, monitor closely
	Azathioprine	Similar toxicity profiles between agents	Enhanced bone marrow toxicity	Avoid combination
	Probenecid	Inhibits renal tubular secretion	Increases mycophenolate mofetil serum concentrations	Decrease mycophenolate mofetil dose
	Salicylates	Protein binding displacement of mycophenolate mofetil	Increases free fraction of mycophenolate mofetil	Only seen when high doses of salicylates are used, may need to decrease mycophenolate dose

Table 5 (cont'd)
Potential Drug Interactions with Immunosuppressant Agents

Immunosuppressant	Interacting Agent(s)	Mechanism	
Cyclosporine	Erythromycin, metoclopramide ^a	Erythromycin inhibits cytochrome P450 enzymes in the intestinal mucosa and liver. Metoclopramide mechanism unclear	
	Diltiazem, nifedipine, verapamil, azoles, erythromycin, oral contraceptives, tacrolimus, amiodarone ^a	Inhibit hepatic and intestinal cytochrome P450 3A4 enzymes	
	Octreotide, phenytoin, rifampin, cholestyramine, probucol ^a	Interfere with intestinal absorption	
	Nafcillin, phenytoin, phenobarbital, carbamazepine, rifampin ^a	Induce hepatic cytochrome P450 IIIA4 enzymes	
	Aminoglycosides, amphotericin B, NSAIDs, acyclovir, ganciclovir, ACE inhibitors ^a	Similar toxicity profiles to cyclosporine	
	Nifedipine, phenytoin, diltiazem	Similar toxicity profiles to cyclosporine	
	Minoxidil, prednisone	Similar toxicity profiles to cyclosporine	
	Statins	Similar toxicity profiles to cyclosporine	
	Alcohol, prednisone, progestins, isotretinoin, thiazides, beta-blockers	Similar toxicity profiles to cyclosporine	
	Muromonab-CD3	Other immunosuppressants ^b Indomethacin	Similar effects on immune system
			Similar toxicity to OKT3

^a Also seen with tacrolimus and sirolimus

^b Also seen with antithymocyte globulins (ATGAM and thymoglobulin)

Table 6
Nonprescription Medication Recommendations for Commonly Encountered Ailments

Symptoms	Recommendations	What to Avoid	Reason
Headache, fever or malaise	Acetaminophen	NSAIDs, Aspirin	Increase risk of GI bleeds and acute renal failure
Sneezing, itching, or runny nose	Chlorpheniramine or brompheniramine	Diphenhydramine	Oversedation
Nasal and sinus congestion	Oxymetazoline nasal spray, 0.9% saline nasal spray, phenylephrine nasal spray	Pseudoephedrine or phenylpropanolamine (PPA; currently not on U.S. market)	Increase blood pressures, increase stroke with PPA
Chest congestion	Guaifenesin	Pseudoephedrine or PPA (currently not on U.S. market)	Increase blood pressures, increase stroke with PPA
Productive cough	Guaifenesin	Cough syrups with sugar	Increase hyperglycemia
Dry cough	Dextromethorphan, codeine	Cough syrups with sugar	Increase hyperglycemia
Constipation	Psyllium, docusate, bisacodyl	Overuse of stimulant products	Dependence on stimulant for regular bowel function
Diarrhea	Loperamide	Bismuth, attapulgite	Causes inconsistent absorption of immunosuppressants
Stomach upset	Calcium carbonate	Magnesium-based medication, aluminum-based products, bismuth	Causes inconsistent absorption of immunosuppressants, in chronic use aluminum products cause osteomalacia
Stomach upset from over acid secretion	Ranitidine, famotidine, nizatidine	Cimetidine	Potential drug interactions
Gas	Simethicone	Alpha-galactosidase enzymes, magnesium-based medications	Can increase hyperglycemia and causes inconsistent absorption of immunosuppressants
Insomnia	Diphenhydramine, doxylamine	Combination cold/sleep preparations containing 25% alcohol	High alcohol content

SELECTED REFERENCES AND SUGGESTED READINGS

General Reviews

1. Mitchison HC, Neuberger JM. Medical complications of liver transplantation. *Dig Dis*. 1993;11:78–101.
2. Silkensen JR. Long-term complications in renal transplantation. *J Am Soc Nephrol*. 2000;11:582–588.
3. Rao VK. Post-transplant medical complications. *Surg Clin North Am*. 1998;78:113–132.

Infections

1. Fishman JA, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med*. 1998;338:1741–1751.
2. Singh N. Infectious diseases in the liver transplant recipient. *Semin Gastrointest Dis*. 1998;9:136–146.
3. Dummer S, Kusne S. Liver transplantation and related infections. *Semin Respir Infect*. 1993;8:191–198.
4. Hibberd PL, Rubin RH. Renal transplantation and related infections. *Semin Respir Infect*. 1993;8:216–224.
5. Branten AJ, Beckers PJ, Tiggeler RG, Hoitsma AJ. Pneumocystis carinii pneumonia in renal transplant recipients. *Nephrol Dial Transplant*. 1995;10:1194–1197.
6. Couchoud C, Cucherat M, Haugh M, Pouteil-Noble C. Cytomegalovirus prophylaxis with antiviral agents in solid organ transplantation: a meta-analysis. *Transplantation*. 1998;65:641–647.
7. Smith SR, Butterly DW, Alexander BD, Greenberg A. Viral infections after renal transplantation. *Am J Kidney Dis*. 2001;37:659–676.

Long-term Immunosuppressive Strategies

1. Helderma JH, Van Buren DH, Amend WJ Jr., Pirsch JD. Chronic immunosuppression of the renal transplant patient. *J Am Soc Nephrol*. 1994;4(suppl 8):S2–S9.

2. Mathew TH. Optimal long-term immunotherapy protocols. *Transplant Proc*. 1999;31:1102–1103.
3. McMaster P, Gunson B, Min X, Afonso R, Bastos J. Liver transplantation: changing goals in immunosuppression. *Transplant Proc*. 1998;30:1819–1821.
4. Riordan SM, Williams R. Tolerance after liver transplantation: does it exist and can immunosuppression be withdrawn? *J Hepatol*. 1999;31:1106–1119.

Osteoporosis

1. Epstein S, Shane E, Bilezikian JP. Organ transplantation and osteoporosis. *Curr Opin Rheumatol*. 1995;7:255–261.
2. Coen G. Fracturing osteoporosis after kidney transplantation—what are the options? *Nephrol Dial Transplant*. 1996;11:567–569.
3. McCaughan GW, Feller RB. Osteoporosis in chronic liver disease: pathogenesis, risk factors, and management. *Dig Dis*. 1994;12:223–231.
4. American College of Rheumatology Task Force on Osteoporosis Guidelines. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheum*. 1996;39:1791–1801.

Post-transplant Diabetes Mellitus

1. Jindal RM, Sidner RA, Milgrom ML. Post-transplant diabetes mellitus: the role of immunosuppression. *Drug Saf*. 1997;16:242–257.
2. Jindal RM. Post-transplant diabetes mellitus—a review. *Transplantation*. 1994;58:1289–1298.
3. Navasa M, Bustamante J, Marroni C, et al. Diabetes mellitus after liver transplantation: prevalence and predictive factors. *J Hepatol*. 1996;25:64–71.

Malignancy

1. Savage P, Waxman J. Post-transplant lymphoproliferative disease. *QJM*. 1997;90:497–503.
2. Penn I. Tumors after renal and cardiac transplantation. *Hematol Oncol Clin North Am*. 1993;7:431–445.

3. Sheil AG. Patterns of malignancies following renal transplantation. *Transplant Proc.* 1999;31:1263–1265.
4. Tan-Shalaby J, Tempero M. Malignancies after liver transplantation: a comparative review. *Semin Liver Dis.* 1995;15:156–164.

Acute/Chronic Rejection

1. Suthanthiran M, Strom TB. Mechanisms and management of acute renal allograft rejection. *Surg Clin North Am.* 1998;78:77–94.
2. Ponticelli C. Progression of renal damage in chronic rejection. *Kidney Int.* 2000;57(suppl 75):S62–S70.
3. Jindal RM, Hariharan S. Chronic rejection in kidney transplants: an in-depth review. *Nephron.* 1999;83:13–24.
4. Hayry P, Aavik E, Savolainen H. Mechanisms of chronic rejection. *Transplant Proc.* 1999;31(suppl 7A):5S–8S.
5. Tilney NL, Kusaka M, Pratschke J, Wilhelm M. Chronic rejection. *Transplant Proc.* 1998;30:1590–1594.
6. Knechtle SJ. Rejection of the liver transplant. *Semin Gastrointest Dis.* 1998;9:126–135.

Recurrence of Disease

1. Mathew TH. Recurrence of disease following renal transplantation. *Am J Kidney Dis.* 1988;12:85–96.
2. Reich D, Rothstein K, Manzarbeitia C, Muñoz S. Common medical diseases after liver transplantation. *Semin Gastrointest Dis.* 1998;9:110–125.
3. McGory RW, Ishtani MB, Oliveira WM, et al. Improved outcome of orthotopic liver transplantation for chronic hepatitis B cirrhosis with aggressive passive immunization. *Transplantation.* 1996;61:1358–1364.
4. Lumbreras C, Colina F, Loinaz C, et al. Clinical, virological, and histological evolution of hepatitis C virus infection in liver transplant recipients. *Clin Infect Dis.* 1998;26:48–55.

Immunizations

- a. Grabenstein JD, Baker JR. Immunization and organ transplantation. *Hosp Pharm.* 1999;339–

351.

- b. Harmon WE. Immunization practices in transplant recipients. *Lit Scan Transpl.* 2000;16:4–5.

OTCs, Medication Non-adherence, and Drug-Drug and Drug-Herb Interactions

1. Smolinske SC. Dietary supplement-drug interactions. *J Am Med Womens Assoc.* 1999;54:191–192, 195.
2. Trotter JF. Drugs that interact with immunosuppressant agents. *Semin Gastrointest Dis.* 1998;9:147–153.
3. Lake KD, Canafax DM. Important interactions of drugs with immunosuppressive agents used in transplant recipients. *J Antimicrob Chemother.* 1995;36(suppl B):11–22.
4. Fugh-Berman A. Herb-drug interactions. *Lancet.* 2000;355:134–138.
5. Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med.* 1998;158:2200–2211.
6. Ellingson T, Wipke-Tevis D, Messina C, Livesay T. The use of over-the-counter medications by transplant recipients: a guideline. *J Transpl Coord.* 1999;9:17–24.
7. Newton SE. Promoting adherence to transplant medication regimens: a review of behavioral analysis. *J Transpl Coord.* 1999;9:13–16.

Development of a Patient Care Plan and Reimbursement for Provision of Pharmaceutical Services

1. McCallian DJ, Carlstedt BC, Rupp MT. Elements of a pharmaceutical care plan. *J Am Pharm Assoc (Wash).* 1999;39:82–83.
2. Canaday BR, Yarborough PC. Documenting pharmaceutical care: creating a standard. *Ann Pharmacother.* 1994;28:1292–1296.
3. Poirier S, Buffington DE, Memoli GA. Billing third party payers for pharmaceutical care services. *J Am Pharm Assoc (Wash).* 1999;39:50–64.
4. Rupp MT. Standardizing documentation for filing pharmaceutical care claims. *Am Pharm.* 1995;NS35:26–30.

Exam Questions

Implementing Patient Care Management: Acute and Chronic Care of the Kidney or Liver Transplant Recipient

Robert E. Dupuis, Pharm.D., BCPS, David Taber, and Amy Fann

CHOOSE THE CORRECT ANSWER

To obtain continuing education credits, please choose the correct answer. A score of 70% is required for certification. Should you score less than 70%, no certification will be mailed.

- 1. The most commonly used antimicrobial regimen in the liver transplant patient during the perioperative period to prevent infection is:**
 - a. Ampicillin/sulbactam
 - b. Third-generation cephalosporins
 - c. Ampicillin/cefotaxime
 - d. Sulfamethoxazole-trimethoprim
- 2. The bacteria most commonly associated with intra-abdominal and wound infections in liver transplant patients during the perioperative period originate from:**
 - a. Skin
 - b. Airborne
 - c. Intestinal lumen flora
 - d. Both a and c are correct
 - e. All of the above are correct
- 3. The most common source of infection within the first two weeks after kidney transplantation is:**
 - a. Intestinal lumen flora
 - b. Skin
 - c. Airborne pathogens
 - d. Both a and b are correct
 - e. All of the above are correct
- 4. Which of the following pathogens is NOT commonly responsible for causing urinary tract infections (UTIs) in post-kidney transplant patients?**
 - a. Streptococci
 - b. Staphylococcus aureus
 - c. Escherichia coli
 - d. All commonly produce UTIs in these patients
- 5. The differential diagnoses of acute kidney rejection include all of the following, EXCEPT:**
 - a. Infection
 - b. Dehydration
 - c. Recurrence of primary disease
 - d. Calcineurin inhibitor toxicity
 - e. All of the above warrant consideration
- 6. The definitive diagnosis of acute rejection for both liver and kidney transplant is made by:**
 - a. Signs and symptoms
 - b. Laboratory testing (e.g., creatinine, ALT, AST, and bilirubin levels)
 - c. Tissue biopsy
 - d. All of the above

7. **Patient education and discharge planning should include which of the following elements?**
 - a. Medication use
 - b. Measuring and recording temperature
 - c. Lifestyle habits
 - d. Contact information of principal care providers
 - e. All of the above

8. **Long-term graft failure in kidney recipients is most commonly a consequence of:**
 - a. Recurrence of primary disease
 - b. Cardiovascular disease
 - c. Chronic rejection
 - d. Both b and c are correct
 - e. All of the above are correct

9. **What is considered first-line treatment of CMV disease in solid organ transplant patients?**
 - a. Foscarnet
 - b. IV ganciclovir
 - c. CMV hyperimmune globulin
 - d. Nonspecific immunoglobulins in combination with antiviral agents

10. **Which laboratory test provides the best clue of clinical CMV disease, particularly in patients not receiving prophylactic therapy?**
 - a. PCR serology
 - b. Shell viral assay
 - c. CMV antigenemia
 - d. All of the above

11. **The most critical period of bone loss after solid-organ transplantation is:**
 - a. First month post-transplant
 - b. First 6 months
 - c. First year
 - d. Long-term, chronic bone loss

12. **Which of the following statements is FALSE concerning post-transplant diabetes mellitus (PTDM)?**
 - a. The incidence of PTDM is approximately 4% to 20%
 - b. Tacrolimus is an inducer of insulin resistance
 - c. Cyclosporine inhibits cellular proteins resulting in decreased insulin production
 - d. Corticosteroids decrease the number and affinity of insulin receptors
 - e. Transplant patients should be educated on the same issues as a patient with diabetes mellitus

- 13. Which of the following statements regarding malignancy in transplant patients is FALSE?**
- The average age of diagnosis is 42 years
 - Overall incidence is 6%, 20-50 times more than other patient populations
 - The most common types of malignancies in transplant recipients are cancers of the skin and lips, and non-Hodgkin's lymphoma (NHL)
 - NHL responds favorably to chemotherapy
 - Immunosuppression and presence of EBV are major risk factors for the development of NHL
- 14. Use of drugs that inhibit or induce the cytochrome P40 3A4 enzyme system are contraindicated in transplant recipients, as they will interfere with immunosuppressive and prophylactic antimicrobial therapies.**
- True
 - False
- 15. With regard to immunizations and transplant recipients, which of the following statements is FALSE?**
- Prior to transplantation, all immunizations should be brought up to date
 - Influenza vaccination appears to be effective in post-transplant patients
 - The use of varicella zoster vaccination in pre-transplant pediatric patients is recommended to prevent complications post-transplant
 - Post-transplant vaccination against Hepatitis B is recommended because the vaccine produces lower antibody response post-transplant
- 16. A liver transplant recipient, 2-months post-transplant, complains of headaches. He calls you to inquire about an appropriate OTC analgesic that won't interfere with his current immunosuppressive regimen. Which of the following would you recommend this patient?**
- Aspirin
 - NSAID (e.g., ibuprofen)
 - Aspirin/Caffeine tablet
 - Acetaminophen
 - All of the above would be considered appropriate
- 17. A patient, 1-month post-transplant, calls to complain of diarrhea, which started the day before and has not subsided with the use of Pepto-Bismol®. Which of the following statements is TRUE concerning this patient?**
- Recommend that the patient increase the dose of Pepto-Bismol, because of interaction with his immunosuppressants
 - Recommend a switch to Kaopectate® or Donnagel® because of potential drug-drug interactions with the Pepto-Bismol
 - Recommend a switch to loperamide as this product will not interfere with the absorption of immunosuppressant medications
 - All of the above statements are false

- 18. Although diphenhydramine is not contraindicated in a transplant recipient, and is currently recommended for use in treating insomnia, it should be avoided in patients suffering mild allergy symptoms.**
- True
 - False
- 19. Which of the following statements is FALSE concerning opportunistic infections post-transplant?**
- Pneumocystis carinii infection can occur frequently despite adequate prophylaxis
 - Candida albicans infection usually occurs within the first month post-transplant
 - First-line preventative therapy against pneumocystis carinii pneumonia usually is effective in preventing the onset of urinary tract infections
 - There is a recent rise in the incidence of fluconazole-resistant Candida albicans
 - First-line therapy for the prevention of Thrush is nystatin
- 20. Which of the following statements is FALSE concerning the use of herbal products in transplant recipients?**
- St. John's Wort may lead to graft rejection because it can reduce cyclosporine levels
 - Echinacea can be used to supplement therapy because of its immunosuppressive properties
 - Ginkgo biloba may increase the risk of bleeding
 - Ginseng should be avoided as it may augment the effects of corticosteroids

Program Evaluation

Please assist us in evaluating the quality of this publication by completing the following evaluation. On a scale of 1 to 5, with 1 being the best understanding of this subject matter, please rate the knowledge you gained from this educational activity.

1. Can you define the role of the pharmacist and other healthcare professionals in the postsurgical care of a transplant patient?

1 2 3 4 5

2. Do you understand the necessary mechanisms required to ensure a seamless transition from in-hospital care to the community setting?

1 2 3 4 5

3. Can you implement the patient care models for the ongoing monitoring and care by pharmacists and other providers in acute, ambulatory, clinic, and community settings?

1 2 3 4 5

5. Overall, do you feel this activity met the goals and objectives for this program?

1 2 3 4 5

6. Please rate the level of difficulty of the information presented.

Too Simple Simple Appropriate Difficult Too Difficult