

Recommendations for the Outpatient Surveillance of Renal Transplant Recipients

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Abstract. Many complications after renal transplantation can be prevented if they are detected early. Guidelines have been developed for the prevention of diseases in the general population, but there are no comprehensive guidelines for the prevention of diseases and complications after renal transplantation. Therefore, the Clinical Practice Guidelines Committee of the American Society of Transplantation developed these guidelines to help physicians and other health care workers provide optimal care for renal transplant recipients. The guidelines are also intended to indirectly help patients receive the access to care that they need to ensure long-term allograft survival, by attempting to systematically define what that care encompasses. The guidelines are applicable to all adult and

pediatric renal transplant recipients, and they cover the outpatient screening for and prevention of diseases and complications that commonly occur after renal transplantation. They do not cover the diagnosis and treatment of diseases and complications after they become manifest, and they do not cover the pretransplant evaluation of renal transplant candidates. The guidelines are comprehensive, but they do not pretend to cover every aspect of care. As much as possible, the guidelines are evidence-based, and each recommendation has been given a subjective grade to indicate the strength of evidence that supports the recommendation. It is hoped that these guidelines will provide a framework for additional discussion and research that will improve the care of renal transplant recipients.

The morbidity and mortality rates associated with renal transplantation and the use of immunosuppressive medications are high. However, many posttransplant complications can be prevented, or at least more effectively treated, if they are detected earlier, rather than later. Guidelines have been developed for the prevention of diseases in the general population, but there are no comprehensive guidelines for the prevention of diseases and complications after renal transplantation. In addition, whether general disease prevention strategies and guidelines developed for the general population are applicable to transplant recipients has not been addressed in a systematic manner.

The recent emphasis on cost-cutting in medicine has created an impetus for health plans to develop guidelines designed to reduce expenditures. Unfortunately, guidelines developed by payers are rarely evidence-based and may not be primarily focused on optimizing patient outcomes. The American Society of Transplantation (AST) conducted a survey of medical and surgical directors of United Network for Organ Sharing (UNOS) renal transplant centers. Of the 117 respondents, 97% agreed that there was a need for recommendations guiding the surveillance of renal transplant recipients (R.S. Gaston, B.L. Kasiske, R.J. Tesi, G.M. Danovitch, and M.J. Bia, unpublished observations). The AST Board of Directors also concluded that there is a need for evidence-based recommendations designed to reduce the burden of disease after renal transplantation, in a cost-effective manner. It was also recognized that guidelines could indirectly help patients receive the access to care that they need to ensure long-term allograft survival. Therefore, the Board asked the AST Clinical Practice Guidelines Committee to develop recommendations for the outpatient surveillance of renal transplant recipients.

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Scope

These guidelines are applicable to all (adult and pediatric) renal transplant recipients. They cover outpatient screening for and prevention of diseases and complications that commonly occur after renal transplantation. They do not cover the diagnosis and treatment of diseases and complications after they become manifest. They do not cover the pretransplant period, and guidelines for the evaluation of renal transplant candidates have been published (1). They do not address the choice of immunosuppressive medications and cover only outpatient monitoring for and prevention of complications. They do not cover the treatment or prevention of renal allograft rejection. In addition, the guidelines do not cover every aspect of screening and prevention, and omissions should not be construed as recommendations for avoiding particular screening measures or preventive strategies.

Intended Users

These guidelines were designed to be used by physicians and health care workers who care for renal transplant recipients in the outpatient clinics of kidney transplant centers. They were not specifically developed for primary care physicians; however, local referring physicians may find them useful. In addition, these guidelines may be helpful for trainees at all levels who wish to learn about renal transplantation. To the extent that these guidelines are evidence-based, they may also be useful for those seeking to identify future research needs. Finally, we recognize that some health care planners and providers may find that the guidelines help them to understand what is involved in the optimal treatment of renal transplant recipients.

Materials and Methods

The committee searched the medical literature and reviewed pertinent publications. Searches were conducted using Medline and recent pertinent bibliographies. An electronic database was used to collate references, but no systematic data extraction or synthesis was performed. A draft of recommendations was developed using the expertise of committee members and the results of the literature review. This draft was sent to societies and individuals for review and suggested modifications. In particular, the draft was sent to the Council of American Kidney Societies and its non-AST member organizations, including the American Society of Nephrology, the Renal Physicians Association, the American Society of Pediatric Nephrology, and the National Kidney Foundation. The draft was also sent to individuals who are recognized experts in areas covered by the recommendations; the experts were specifically asked for their input. Taking into account the suggestions made by these organizations and individuals, a final draft was written and submitted to the AST Board for approval. It is anticipated that the reliability of these recommendations will diminish after 3 yr, at which time they will need to be updated.

We graded the strength of the evidence supporting each recommendation using the system developed by the Canadian Task Force on the Periodic Health Examination (2) and adopted by the United States Preventive Services Task Force (3). Accordingly, recommendations were graded A, B, C, D, or E as follows: A, there is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination; B, there is fair evidence to

support the recommendation that the condition be specifically considered in a periodic health examination; C, there is poor evidence regarding the inclusion of the condition in a periodic health examination, but recommendations may be made on other grounds; D, there is fair evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination; E, there is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

Organizational Scheme

The guidelines are organized in sections and tables. Most tables indicate the incidence of the disease or complication being screened, the consequences of the disease or complication, the rationale for screening and/or prophylaxis, and specific recommendations. Each table is followed by a detailed discussion, which may include a definition of the disease or complication and discussions of the incidence, the consequences, and the rationale for screening or prophylaxis. Table 1 is a table of contents.

I. Frequency and Timing of Outpatient Visits (Table 2)

There are virtually no scientific data on which to base decisions regarding the optimal frequency or type of contact between renal transplant recipients and transplant centers. Most outpatient encounters occur on the basis of circumstances and experiences that may be unique to each patient population and individual transplant center. To better understand current practices, we conducted a survey of medical and surgical directors of UNOS renal transplant centers.

Respondents to the survey reported that three-quarters of adult renal allograft recipients leave the hospital within 8 d after transplantation. Although the issue was not addressed in the survey, pediatric patients generally require longer hospitalizations (4). Virtually all patients return home, although some centers maintain nearby facilities for patients living a long distance away. In the AST survey, 80% of centers reported monitoring patients two or three times each week during the first 1 mo after transplantation. Between 1 and 3 mo after transplantation, 86% of centers continue to monitor recipients on at least a weekly basis. During this early posttransplant period, the risk of acute rejection and graft loss is at its peak (5). Accordingly, immunosuppression is most intense during this time. The overall risk of adverse immunologic and non-immunologic events during this period, combined with the relatively asymptomatic nature of most rejection episodes, suggests that frequent monitoring is warranted. In 75% of centers responding to the AST survey, a transplant physician or surgeon provides care during the first 3 mo.

After the first 3 mo, when and by whom patients are monitored vary widely among transplant centers. The role of transplant surgeons diminishes, in terms of the amount of outpatient care provided. Transplant physicians become the primary caregivers at some transplant centers, whereas the majority of care is provided elsewhere, usually by referring physicians, at other centers. Most recipients (4 to 12 mo after transplantation) are examined at least monthly, with 65% of outpatient visits oc-

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curing at the transplant center. The primary focus of visits during this period is ongoing surveillance for acute rejection, infection (the highest risk of opportunistic infections occurs between 1 and 6 mo after transplantation), and immunosuppressive agent toxicity (6–8).

For patients with functioning allografts after 12 mo, issues and practices change. The risk of acute rejection, in the absence of therapy nonadherence, is small. Immunosuppressive medication dosing for most patients requires only infrequent monitoring and adjustment. Common practice is for patients to

Table 2. Frequency and timing of outpatient visits

Time after transplantation	Interval for routine visits ^a	Rationale
First 30 d	2 to 3/wk	Screen for acute rejection (high risk), postoperative complications, and adverse effects of immunosuppressive medications
1–3 mo	1 wk (children), 1 to 3 wk (adults)	Screen for acute rejection (high risk), opportunistic infections, adverse effects of immunosuppressive medications, and adherence (especially children)
4–12 mo	2 to 4 wk (children), 4 to 8 wk (adults)	Screen for acute rejection (moderate risk), opportunistic infections, adverse effects of immunosuppressive medications, adherence (especially children), and growth and development (children)
>12 mo	1 mo (children), 2 to 4 mo (adults) 3 to 6 mo	Screen for graft dysfunction Screen for graft dysfunction, cardiovascular disease risk, cancer, adverse effects of immunosuppressive medications, general health maintenance, adherence, and growth and development (children)

^a Visits may be for laboratory tests only or may include contact with transplant nurses, coordinators, and/or physicians, as deemed necessary by either the patient or caregivers.

undergo outpatient visits every 3 to 6 mo (as reported by 62% of the centers responding to the AST survey); however, 25% of centers continue to monitor patients monthly. Only approximately one-half of these visits occur at the transplant center. The primary focus of these “late” encounters is ongoing surveillance of allograft function (with careful attention to allograft function and urinary protein excretion), as well as re-evaluation of the immunosuppressive regimen in terms of efficacy, toxicity, and cost (9–11). If patients experience problems, prompt attention is most likely to yield effective results. Problems detected by transplant physicians or other primary providers usually result in visits to the transplant center.

Pediatric patients require different schedules of surveillance. These differences are based on the unique complications and outcomes of pediatric renal transplant recipients. The incidence of acute rejection episodes is higher among children than among adults, and rejection may be more difficult to diagnose, particularly if there is a large difference in size between the donor and the recipient (12,13). Also, the metabolism of many immunosuppressive medications is substantially different in young children, compared with adults, and drug metabolism changes as children grow and develop. Furthermore, the incidence and severity of nonadherence are thought to be higher among adolescents than among adults. The growth and development of children are adversely affected by graft dysfunction and by some of the commonly used immunosuppressive medications, necessitating frequent monitoring and adjustment. Children frequently exhibit urologic abnormalities as the cause of end-stage renal disease (ESRD), which may require reconstructive surgery before or after renal transplantation (4). Therefore, they require careful assessment for urinary tract infections and monitoring of bladder and genitourinary function. Some reports have demonstrated better outcomes if the

care of children is provided by specialized pediatric renal transplant centers (14–17).

Recent improvements in short-term graft survival rates have resulted in a larger number of patients being exposed to the risks of late complications (5,18). Maximization of long-term patient survival rates requires the ongoing management of cardiovascular disease (CVD) risk factors, such as hyperlipidemia and hypertension, as well as screening for cancer and other complications that are directly or indirectly linked to immunosuppression. Because of the complexity of current immunosuppressive regimens and the high incidence of adverse drug effects and drug interactions, an experienced transplant physician should be involved in the long-term care of transplant recipients.

There are a number of reasons why relatively frequent visits to the transplant center may improve long-term outcomes. Chronic allograft failure, death with a functioning allograft, and nonadherence account for the great majority of late graft losses. The effects of each of these factors may be diminished by frequent visits to the transplant center. With respect to nonadherence, effective immunosuppressive regimens have greatly reduced early graft loss and have enabled a growing number of recipients to achieve long-term graft survival, despite the fact that they remain at high risk for allograft rejection. It is ironic that the effectiveness of immunosuppressive medications administered to prevent early rejections has resulted in more recipients being dependent on these potent drugs to maintain long-term graft function. Consequently, the relative effects of nonadherence on graft outcomes is becoming greater (19–21). Data gathered in other fields of medicine confirm the importance of frequent encounters between patients and providers in facilitating adherence to therapy. Therefore, efforts to decrease the frequency of outpatient visits to the transplant

center or other providers may be counterproductive. Some data indicate that patients actually dislike long periods between visits; such gaps tend to foster uncertainty regarding the status of the allograft and worries about potential adverse outcomes.

II. Graft Function

Graft Dysfunction (Table 3)

Definition. Most but not all of the adverse consequences of renal failure can be directly attributed to insufficient GFR. Although other functions of the kidney are important, failure of these other functions is rarely observed in the absence of reduced GFR.

Incidence. Epidemiologic studies using large transplant registries have unequivocally demonstrated a progressive loss of renal allografts in the late posttransplant period. Therefore, only patients who die with a functioning allograft will likely escape a decrease in GFR at some time after transplantation.

Consequences. The function of the transplant needs to be estimated repeatedly during the life of the graft. Episodes of acute allograft rejection have been documented in the third decade after transplantation, and allografts are constantly threatened by nonimmunologic injuries that may or may not be reversible. At no time after transplantation can function stability be taken for granted. Clinical signs of rejection and dysfunction are notoriously unreliable, and repeated laboratory testing is required.

Rationale. There are a number of circumstances in which screening for graft dysfunction may alter therapy and benefit the patient. The first is the detection of acute rejection. Generally, the only practical way to detect acute rejection in its early treatable stage is to screen at regular intervals with some direct or indirect measurement of renal function. Acute rejection

often occurs without signs or symptoms. Frequent repetitive allograft biopsies or fine-needle aspiration biopsies are theoretically possible but are less practical. The early recognition of acute rejection and its complete reversal may minimize its unfavorable effects on long-term graft function. The completeness of reversal of graft dysfunction after an episode of acute rejection, as measured by the serum creatinine level, is a prognostic indicator.

The second case is the detection of nephrotoxicity resulting from immunosuppressive medications. Cyclosporine A (CsA) and tacrolimus have become mainstays of immunosuppression after renal transplantation. Both can cause renal toxicity. As in the case of acute rejection, nephrotoxicity can be detected only by screening for changes in renal function. The detection of nephrotoxicity may prompt changes in immunosuppressive medications. Even small changes in the doses of immunosuppressive medications may cause changes in graft function.

The third case is the detection of changes in renal function resulting from obstruction, renal artery stenosis, or other reversible causes of graft dysfunction. Other causes of graft dysfunction may be reversible if detected early and may be detected only if screening tests of renal function are routinely performed.

In the fourth case, chronic renal allograft failure is often evident only from subtle changes in renal function. With time, all kidney transplants are subject to chronic allograft failure, which may occur as early as 6 mo after transplantation (22). Although there is no proof from randomized controlled trials, an increasing amount of evidence suggests that aggressive risk-factor management may help slow the rate of progression of chronic allograft failure (23–31). Controlling BP, reducing urinary protein excretion, treating hyperlipidemia, and maxi-

Table 3. Graft dysfunction

Incidence	Most patients who do not die eventually develop acute and/or chronic graft dysfunction.
Consequences	Graft failure
Rationale	Detection of acute rejection, nephrotoxicity resulting from medications, chronic allograft nephropathy, and renal dysfunction resulting from other causes can suggest therapy that may prolong graft survival. Measuring function can also help predict the need and timing for replacement of renal allografts and can encourage adherence to therapies.
Recommendations	<p>Serum creatinine levels should be used to screen for changes in renal function, and patients should have access to a laboratory that can measure serum creatinine levels and immediately transmit the results to the transplant center (A).</p> <p>For stable adult patients, serum creatinine levels should be measured at least twice weekly in the first month, weekly in the second month, biweekly in the third and fourth months, monthly to the end of year 1, every 2 mo until the end of year 2, and every 3 to 4 mo, thereafter (B).</p> <p>For stable pediatric patients, serum creatinine levels should be measured at least twice weekly in the first 2 mo, weekly in months 3 and 4, every 2 wk in months 5 to 8, and monthly thereafter (B).</p> <p>Patients should be informed of the significance of increases in serum creatinine levels and the need for monitoring (C).</p> <p>A formula that adjusts for factors that may influence the relationship between serum creatinine levels and GFR should be used to estimate GFR at baseline and after subsequent changes in serum creatinine levels (B).</p> <p>Periodic screening with more accurate methods for assessment of GFR is optional (C).</p>

mizing immunosuppression may help slow the rate of progression. Repetitive measurements of renal function may indicate patients with early chronic allograft failure and thereby identify patients who require close management and supervision. In addition, measurements of the rate of progression may help patients and caregivers plan for the eventual need for renal (allograft) replacement therapy.

Finally, it is likely that measuring renal function is a helpful reminder to patients of the possibility of allograft dysfunction and regular measurements of renal function may help encourage patients and remind them to adhere to therapy. At least one study noted that the failure of patients to adhere to prescribed serum creatinine screening was a predictor of late renal allograft failure (32).

Measurement of serum creatinine levels is a simple and inexpensive but invaluable indirect method to detect decreases, especially acute decreases, in GFR. The universal availability of laboratories that can measure serum creatinine levels makes this test particularly useful. The serum creatinine level is also the most valuable prognostic marker of subsequent graft function at all times after transplantation. The interval for measuring serum creatinine levels can be based on the frequency of expected graft dysfunction at different times after transplantation. Most cases of acute rejection and episodes of graft dysfunction occur in the first 2 mo after transplantation.

Pediatric renal transplant recipients experience more acute rejection episodes than do adults (12,13). This may be attributable to increased metabolism of immunosuppressive medications, heightened immune responses, or medication nonadherence. The incidence of late acute rejections may also be higher. As a result, children require more frequent surveillance. The normal range for serum creatinine levels changes with age and body size.

Notwithstanding the practical advantages of using the serum creatinine level as a marker of renal function, it is a relatively inaccurate indicator of the true GFR for renal transplant recipients (33–35). With formulas that take into account clinical parameters that are correlated with muscle mass, serum creatinine levels may more accurately reflect GFR (36–40). However, GFR estimated by using formulas that include serum creatinine levels are also subject to substantial variability (41–43). In addition, many of the variables used in formulas to estimate GFR (*e.g.*, gender, age, height, and body weight) adjust more for differences between patients than for differences that occur in the same patients with time. The latter differences are most critical in the monitoring of renal transplant recipients. However, during long periods of time, changes in muscle mass and the resulting changes in creatinine production make the serum creatinine level a less sensitive marker for detecting chronic decreases in GFR (44). Indeed, studies have demonstrated that the serum creatinine level is relatively unreliable for detecting chronic changes in renal function (33,34,45). Other endogenous markers of GFR, such as the serum cystatin C level (46), may ultimately prove to be superior to the serum creatinine level for detecting acute and chronic changes in renal function, but these markers require

additional testing before they are adopted in routine clinical practice (47).

Urinary creatinine clearance determinations may be even less accurate than serum creatinine measurements. This is largely attributable to the difficulty of obtaining accurate timed urine collections. In addition, tubular secretion of creatinine results in systematic overestimation of the true GFR for renal transplant recipients (42,48). This overestimation of the GFR can be reduced by blocking tubular secretion of creatinine with cimetidine (49–52). Nevertheless, the usefulness of urinary creatinine clearance measurements is limited.

Urinary and plasma clearance methods that use isotopic or nonisotopic markers of GFR are most accurate. Plasma clearance tests are relatively simple to perform and do not require accurate (and difficult-to-obtain) urine collections. Even methods that use only a single plasma sampling time after injection are reasonably accurate and generally acceptable for clinical practice (48,53,54). Although clearance of isotopic agents can also be measured with a gamma camera positioned over the allograft (55,56), this approach is more cumbersome and expensive.

It can be argued that the detection of chronic decreases in GFR is not critical for the treatment of transplant recipients, because few therapeutic options are available. This line of reasoning holds that it is generally not necessary to routinely measure renal function by more accurate techniques that use isotopic or nonisotopic markers of GFR. However, these tests may be valuable to assess the significance of changes in serum creatinine levels with time and to provide more accurate baseline levels for follow-up monitoring. A growing body of evidence (albeit largely circumstantial) suggests that at least some therapies may delay the progression of chronic allograft failure (23–31). Therefore, detecting even small, gradual, progressive decreases in GFR may prompt patients and caregivers to be even more diligent in managing immunologic and nonimmunologic risks for graft failure. Finally, these more accurate techniques are often needed to assess the true GFR in planning for subsequent dialysis or repeat transplantation. UNOS currently mandates that patients cannot begin to accrue waiting time points on the cadaveric transplant waiting list until their measured or estimated creatinine clearance values are ≤ 20 ml/min.

Proteinuria (Table 4)

Definition. Transient proteinuria is common and is often observed in association with episodes of acute allograft rejection. Transient proteinuria may not affect allograft or patient survival independent of its underlying cause. Persistent proteinuria is usually defined as protein excretion of >0.5 to 1.0 g/24 h for at least 3 to 6 mo.

Incidence. A number of epidemiologic studies have examined the incidence of persistent proteinuria among renal transplant recipients. In those studies, the incidence of proteinuria (variously defined) ranged from 10 to 25% (57–67).

Consequences. The capacity to excrete urine that is virtually free of filtered protein is a critical function of healthy kidneys. Proteinuria is a manifestation of renal dysfunction

Table 4. Proteinuria^a

Incidence	Ten to 25% of patients exhibit proteinuria of >1 g/24 h for ≥6 mo.
Consequences	Although transient proteinuria, resulting from acute rejection or other causes, may not be associated with decreased graft survival rates, persistent proteinuria is. Causes of persistent proteinuria include chronic allograft nephropathy, transplant glomerulopathy, glomerulonephritis (<i>de novo</i> or recurrent), diabetic nephropathy, and CsA nephrotoxicity.
Rationale	The incidence is high enough to give screening tests sufficient positive and negative predictive values. The consequences of persistent proteinuria are of sufficient magnitude to make screening a useful prognostic test. Treatments to diminish the adverse consequences associated with persistent proteinuria are available.
Recommendations	A baseline determination should be obtained in the first 2 wk after transplantation or as soon as the patient is in stable condition. Thereafter, patients should be screened at least every 3 to 6 mo for the first 1 yr and then every 6 to 12 mo (A). Patients at risk for recurrent, idiopathic, focal, segmental glomerulosclerosis should be screened at least every 2 wk for the first 2 mo after transplantation (B). Dipsticks that measure protein concentrations are suitable for screening, although protein/creatinine ratios are more accurate (B). A dipstick reading of 1+ or greater should prompt repeat testing and/or quantification with protein/creatinine ratio measurements or a timed urine collection test (A). There is insufficient evidence for or against screening for urine albumin excretion (C).

^a CsA, cyclosporin A.

and, when heavy, has important consequences for extracellular fluid volume regulation. The degree of proteinuria also has prognostic and diagnostic implications. Heavy proteinuria is often associated with more rapid deterioration of renal function and is more likely to be associated with pathologic glomerular lesions than with interstitial lesions or anatomic or hemodynamic causes of renal dysfunction (10,59,60,62–66). The most common causes are chronic allograft nephropathy and recurrent or *de novo* glomerulonephritis (57–63,65). Recurrent diabetic nephropathy is likely to become an increasingly common cause of proteinuria as the number of diabetic patients with long-term graft survival increases. Recently, experimental data suggested that proteinuria itself may cause renal injury (68,69). Therefore, it is possible that the often-reported clinical association between proteinuria and the rate of renal function decrease (70) could be, in part, a direct result of injurious effects of proteinuria. A number of studies in the general population have suggested that proteinuria is an important risk factor for CVD (71–73).

Rationale. Indications for and methods of screening for proteinuria were recently reviewed in a position paper by the National Kidney Foundation (74). The prevalence of proteinuria among renal transplant recipients is high enough to give screening tests sufficient positive and negative predictive values. The consequences of new-onset persistent proteinuria are of sufficient magnitude to make screening a useful prognostic test. Treatment that may diminish the adverse consequences of proteinuria is available (25,75–79). Many of the reasons for screening in high-risk populations that were outlined in the National Kidney Foundation position paper can be extrapolated to renal transplant recipients. However, it should be kept in mind that diseased native kidneys may often contribute to low

levels of proteinuria and may occasionally account for large amounts of urinary protein excretion.

Screening for proteinuria is probably best performed with a spot, first-voided, morning urine sample, to negate effects of postural proteinuria, but this may not be practical. The urine dipstick test is a convenient, inexpensive, readily available screening test. It provides an estimate of the urine total protein concentration, which is an indirect measure of urinary protein excretion. The urine protein concentration can be influenced not only by the protein excretion rate but also by the urine concentration (80). Therefore, the interpretation of dipstick results should take into account the urine volume, which may dilute the protein concentration. A 1+ or trace result for a dilute urine sample (*e.g.*, specific gravity of 1.010) likely indicates more protein excretion than does a 1+ or trace result for a concentrated urine sample (*e.g.*, specific gravity of 1.030) (80). Although the standard dipstick test provides only a semi-quantitative estimate of protein excretion, a result of 1+ or greater typically reflects clinically significant proteinuria.

The urine protein/creatinine ratio provides a more accurate assessment of total protein excretion, largely because it takes into account errors attributable to differences in urine concentrations. Measurement of the urine protein/creatinine ratio is convenient, because it requires only a spot sample. A value of 200 mg protein/g creatinine is generally considered abnormal (74). Studies have indicated that protein/creatinine ratio measurements provide results equivalent in value to 24-h collection data in most cases. However, the definitive measurement of total protein excretion is the 24-h urine collection test. Protein excretion of >200 mg/24 h is considered abnormal (74). This test should be accompanied by urine and serum creatinine level measurements, to permit estimation of GFR and determination

of the completeness of urine collection. The principle disadvantages of the 24-h collection test are its inconvenience and its potential inaccuracy because of poor adherence to correct collection techniques. Patients must be trained in the proper method for collection and must be motivated to adhere to instructions. Results are delayed by the time required for patients to collect the samples.

Patients with glomerular disease should undergo proteinuria measurements just before transplantation, if possible. The possibility that posttransplant proteinuria is attributable to the native kidneys should be considered, especially in the early posttransplant period. After proteinuria is detected, how often proteinuria needs to be measured is dependent on the cause, amount, and management of the proteinuria.

Measurements of urine albumin excretion have not been demonstrated to provide diagnostic or prognostic information that is not provided by measurements of total protein excretion for transplant recipients. Measuring urine albumin excretion may prove to be unnecessary, because the prevalence of clinically significant glomerular proteinuria is very high in the transplant population. How the presence of native kidneys might confound the interpretation of microalbuminuria after renal transplantation is unknown. Additional studies are needed to better define the role, if any, of measuring urine albumin excretion after renal transplantation.

Clinically Silent Allograft Rejection (Table 5)

Definition. The histologic findings of acute allograft rejection, *i.e.*, interstitial infiltrates and mild tubulitis that usually occur in association with an acute deterioration in renal function, may be observed in the absence of renal functional changes.

Incidence. The prevalence of acute rejection in protocol biopsies obtained in the first days to weeks during delayed graft function is 15 to 30% (81–83). The prevalence of clinically silent acute rejection at 3 mo has been reported to be 4% (84), 17% (85), and 27% (86). At 3 mo, borderline acute rejection changes were observed in 31% (84), 71% (85), and 21% (86) of cases. The incidences of subclinical and borderline acute rejection at 6 mo were 24 and 25%, respectively, in one study (86). The prevalence of subclinical acute rejection at 2 yr has been reported to be 9% (87) and 12% (85). Evidence of chronic allograft nephropathy in protocol biopsies performed at 3 mo has been reported to be present in 3% (Banff chronic

grade, ≥ 2) (86), 20% (85), 24% (Banff chronic grade, ≥ 2) (88), and 38.3% (84) of cases. The prevalence of chronic allograft nephropathy in protocol biopsies increases to 50 to 70% by 2 yr (85,87).

Consequences. Preliminary data suggest that clinically silent acute rejection may be associated with an increased incidence of graft dysfunction (86).

Rationale. Renal allograft biopsies are often obtained for the diagnosis and management of decreased allograft function, and biopsies performed in that setting are not considered further in these guidelines for posttransplant screening and surveillance. However, periodic examinations of renal histologic features in the absence of changes in renal function may reveal silent rejection that could jeopardize long-term graft survival. Core needle biopsies performed under ultrasonographic guidance, using disposable, spring-loaded biopsy needles, are generally safe and provide adequate tissue for the detection of acute rejection in adult and pediatric transplant recipients (89–92). Standard histologic techniques are adequate for most cases of acute graft dysfunction.

In a small, randomized, controlled trial, Rush *et al.* (86) found that treatment of subclinical rejection detected by protocol biopsies led to better graft function, compared with standard management without protocol biopsies. They also reported uncontrolled data indicating that additional immunosuppression may decrease the incidence of clinically apparent rejection, without affecting the incidence of subclinical rejection (93). These data suggest that protocol biopsies may be necessary to maximally decrease the incidence of rejection, even with newer, more potent, immunosuppressive regimens. Confirmation of these results may elevate protocol biopsies from a research tool to standard clinical practice (94). Additional studies are needed to confirm the utility and cost-effectiveness of protocol biopsies before their widespread adoption in clinical practice. Performing biopsies in high-risk situations, *e.g.*, before major reductions in immunosuppression, may also be warranted if their utility can be confirmed in well-designed clinical trials.

Fine-needle aspiration cytologic examinations have been proposed as an alternative, less invasive strategy to accomplish the same purpose (95–101). Aspiration biopsy is a technically simple and safe procedure that can rapidly provide valuable information regarding causes of acute graft dysfunction in the early posttransplant period. It is limited by an approximately

Table 5. Clinically silent allograft rejection

Incidence	The prevalence of acute rejection in biopsies obtained during delayed graft function in the first days after transplantation is 15 to 30%. The prevalence of clinically silent acute rejection is 4 to 27% at 3 mo, and 9 to 12% at 2 yr. Evidence of chronic allograft nephropathy can be seen in 25 to 40% of cases at 3 mo and in 50 to 70% at 2 yr.
Consequences	Untreated rejection may lead to graft failure.
Rationale	Detection of clinically silent acute rejection could allow timely intervention.
Recommendations	Protocol biopsies may be useful for detecting silent acute rejection and chronic allograft nephropathy, but additional studies are needed to confirm that they have beneficial effects on outcomes (B).

20 to 30% incidence of inadequate samples and by the necessity for skilled cytologic evaluation. Special stains may permit the diagnosis of cytomegalovirus (CMV) infection, and experimental techniques may suggest preclinical diagnoses of acute rejection. Fine-needle aspiration cytologic examinations are not widely available. Noninvasive experimental techniques for detecting silent rejection, using plasma or urine samples, have not yet entered routine clinical practice.

III. Immunosuppressive Medications

Efficacy and Toxicity of CsA (Table 6)

Incidence. Compared with conventional immunosuppression with azathioprine, CsA reduced the incidence of acute rejection and prolonged graft survival in randomized controlled trials (102–107). Early on, it was appreciated that CsA caused nephrotoxicity. The incidence of CsA nephrotoxicity is variable and poorly defined. Reversible decreases in renal blood flow and GFR are observed for most patients. Acute toxicity characterized by endotheliosis and arteriopathy is less common. Chronic, nonspecific, tubulointerstitial atrophy and fibrosis are probably common, but it is difficult to distinguish these from chronic allograft nephropathy attributable to other causes. Hypertension occurs in 41 to 82% (102,106,107), hypercholesterolemia in 37% (107), hyperuricemia in 35 to 52% (106,107), hyperkalemia in 55% (106), tremor in 12 to 39% (102,104,106,107), gingival hyperplasia in 7 to 43% (102,104,107), diabetes mellitus in 2 to 13% (102,107), and hirsutism in 29 to 44% (102,104) of cases.

Consequences. Failure to prevent acute rejection can lead to allograft failure. The role of acute and chronic CsA nephrotoxicity in causing graft failure is less clear. Some adverse

effects, such as hypercholesterolemia, hypertension, and diabetes mellitus, increase the risk of CVD.

Rationale. The bioavailability of CsA is quite variable. In addition, the therapeutic window for CsA (the range of blood levels at which CsA is efficacious but not toxic) seems to be very narrow. As a result, it is generally not possible to determine the correct dose of CsA for individual patients without measuring blood levels. Numerous studies have demonstrated that low CsA blood levels are correlated with subsequent episodes of allograft rejection and, ultimately, allograft failure (108–123). Studies have also demonstrated that high CsA blood levels tend to be correlated with decreased renal allograft function, presumably as a result of nephrotoxicity (108,110,115–117,124,125). These correlations tend to confirm the biologically plausible notion that efficacy and toxicity are linked to blood levels. The association between blood levels and CsA efficacy and toxicity is inexact. Very high levels are more likely to be associated with nephrotoxicity, whereas low levels are more likely to be associated with acute rejection. However, levels in the relatively wide range between these two extremes are less predictive of efficacy and toxicity. A few studies have even suggested that variability in CsA absorption itself is correlated with chronic allograft rejection and decreased graft survival (126).

A number of factors affect CsA blood levels. These include hemoglobin levels (127,128), serum lipid levels (127–129), age (121,124,128,130), gender (124), hepatic dysfunction (124), time of day (131), and race (128). A large number of medications have also been demonstrated to affect CsA blood levels, and it is extremely important to measure CsA blood levels whenever medications that can interact with CsA are

Table 6. Efficacy and toxicity of CsA

Incidence	Although CsA is effective in preventing acute rejection, most patients experience at least some adverse effects.
Consequences	Inadequate therapeutic levels may lead to acute rejection, whereas very high levels are more likely to be associated with nephrotoxicity. Other adverse effects may occur independently of blood level.
Rationale	Routine monitoring of blood levels helps to determine the dose that maintains maximal efficacy with minimal toxicity. Monitoring for adverse effects that are known to occur frequently can also be used to adjust the dose of CsA and/or prescribe therapies, to minimize the consequences of these adverse effects.
Recommendations	Symptoms of CsA toxicity should be sought during periodic history assessments and physical examinations (A). Renal function, BP, lipoprotein levels, and blood glucose levels should be measured periodically (B). Therapeutic blood level monitoring is beneficial (B). Few studies address the optimal interval for monitoring, but levels should be measured more frequently early after transplantation, after CsA dose changes, during periods of growth in pediatric patients, and when there are changes in medications or other factors that may influence CsA levels (C). Whole-blood trough levels are suitable for screening. Complete pharmacokinetic studies are more reliable than trough levels but are considered optional because of their expense and inconvenience. Single-point estimates of CsA pharmacokinetics may also be more accurate than trough levels and may be a suitable alternative to complete pharmacokinetic studies (C).

prescribed. The inherent intra- and interpatient variability in CsA absorption and metabolism make it necessary to use blood levels to monitor and adjust CsA doses. In general, children metabolize CsA faster than adults, and young children generally require three times/d dosing (132). As children grow, the dose of CsA required to maintain the same therapeutic levels increases (132). Because of these differences in metabolic rates and doses, children usually require more frequent monitoring than adults.

Pharmacokinetic studies are less variable (133), are more closely correlated with dose (109,133), and more accurately predict efficacy and toxicity than do trough blood levels (109,134–136). However, pharmacokinetic studies are inconvenient for patients and expensive to perform. As a result, few clinics routinely perform pharmacokinetic studies. A number of investigators have attempted to render pharmacokinetic studies more practical for day-to-day patient care by demonstrating that the number of blood samples required can be reduced (115,132,137–139). However, these abbreviated pharmacokinetic studies have not yet gained widespread acceptance in clinical practice. Instead, most transplant centers use trough CsA levels for dose adjustments. There are few data to suggest how frequently CsA levels need to be determined. However, because it is well known that absorption and metabolism change rapidly soon after transplantation, levels should be measured more frequently during the first few months after transplantation. Blood levels should also be measured whenever there is a change in medications or other factors that may affect CsA metabolism.

Monitoring of CsA efficacy could theoretically be achieved by developing appropriate pharmacodynamic assays, *e.g.*, by monitoring CsA-suppressible immunologic parameters. Several investigators have attempted to develop pharmacodynamic assays to monitor CsA activity (116,140–147). Although this approach holds great promise, pharmacodynamic monitoring of CsA therapy is generally considered experimental at this time.

A number of adverse effects are attributable to CsA. These include hypertension, hyperlipidemia, glucose intolerance, hypomagnesemia, hyperkalemia, hyperuricemia, gout, gingival hyperplasia, hirsutism, central nervous system toxicity, peripheral neuropathy, and possibly metabolic bone disease. Renal dysfunction, hypertension, hyperlipidemia, glucose intolerance, hypomagnesemia, hyperkalemia, hyperuricemia, gout, and metabolic bone disease are multifactorial, and appropriate screening tests are covered elsewhere in these guidelines. Gingival hyperplasia, hirsutism, central nervous system toxicity (especially tremor), and peripheral neuropathy are all detected by physical examinations. It is essential that patients being treated with CsA be examined periodically by a transplant physician familiar with these and other CsA-related complications. Although the optimal frequency of examination has not been well defined, patients should probably be examined more frequently in the early posttransplant period (Table 2).

There are several different formulations of CsA. The pharmacokinetic characteristics of these formulations vary, and the interpretation of CsA trough levels, for example, may be quite

different for different formulations. A detailed discussion of the specific pharmacokinetic characteristics of each CsA formulation is beyond the scope of these guidelines. However, a number of studies suggest that the microemulsion formulation of CsA, *e.g.*, Neoral (Novartis, Basel, Switzerland), is better absorbed and is associated with reduced intra- and interpatient variability in CsA blood levels, compared with standard CsA preparations, *e.g.*, Sandimmune (Novartis) (148–154). It is possible that microemulsion CsA could be monitored with fewer blood level measurements, compared with the standard CsA formulation; however, there have been no studies correlating outcomes with the frequency of blood level monitoring for any CsA preparation.

Studies suggest that the number of acute rejections is higher, whereas the incidence of adverse events may be no different or even lower, with Neoral *versus* Sandimmune (155). However, a recent meta-analysis suggested that there were differences in the results of blinded, randomized, controlled trials, compared with those of open-label trials (156). In open-label studies, Sandimmune was associated with more adverse events than was Neoral. However, in blinded, randomized, controlled trials, the incidence of adverse events was higher with Neoral, compared with Sandimmune (156). Therefore, the results of that analysis suggest that the lower rate of acute rejection with Neoral, compared with Sandimmune, is accompanied by a higher incidence of adverse events. These results raise the question of whether the reported differences between the two preparations are entirely attributable to higher blood levels with Neoral *versus* Sandimmune, resulting in both lower rejection rates and greater toxicity.

Efficacy and Toxicity of Tacrolimus (Table 7)

Incidence. The efficacy and toxicity of tacrolimus were compared with those of CsA in five randomized controlled trials (157–161) and in a meta-analysis of four of those trials (162). The quality of the studies was poor, with none using blinding and none reporting methods of randomization (162). In those trials patients also received corticosteroids and azathioprine for maintenance of immunosuppression. Tacrolimus had no effect on graft loss or mortality rates at 1 yr (162). The incidence of acute rejection at 1 yr was lower among patients treated with tacrolimus, compared with CsA (odds ratio, 0.52; 95% confidence interval, 0.36 to 0.75) (162). In the two largest trials (159,160), detailed information was provided on the incidences of adverse effects with tacrolimus, *i.e.*, decreased renal function in 35 to 42%, diarrhea in 22 to 44%, constipation in 31 to 35%, vomiting in 13 to 29%, hypertension in 37 to 50%, infections in 72 to 76%, and CMV infection in 14 to 20% of cases. In 3-yr follow-up data, the incidences of CMV infection were similar for patients treated with tacrolimus (19.5%) and those treated with CsA (19.3%) (163). Tremor was more common with tacrolimus (35 to 54%), compared with CsA (12 to 34%) (159,160). However, gingival hyperplasia was more common with CsA (5.3 to 6.2%) than with tacrolimus (0.5 to 1.3%) (159,160). Similarly, hirsutism was more common with CsA (8.7 to 9.7%) than with tacrolimus (0 to 0.5%) (159,160). Three trials reported the prevalence of posttransplant diabetes

Table 7. Efficacy and toxicity of tacrolimus

Incidence	Although tacrolimus is effective in preventing acute rejection, most patients experience at least some adverse effects.
Consequences	Inadequate therapeutic levels may lead to acute rejection, whereas very high levels are more likely to be associated with nephrotoxicity and posttransplant diabetes. Other adverse effects may occur independently of blood levels.
Rationale	Routine monitoring of blood levels helps to determine the dose that maintains maximal efficacy with minimal toxicity. Monitoring for adverse effects that are known to occur frequently can also be used to adjust the dose of tacrolimus and/or prescribe therapies, to minimize the consequences of these adverse effects.
Recommendations	Evidence of toxicity should be sought during periodic history assessments and physical examinations (A). Renal function, BP, and blood glucose levels should be measured periodically (B). Therapeutic blood level monitoring is beneficial (B). Few studies address the optimal interval for monitoring, but levels should be measured more frequently early after transplantation, after dose changes, and when there are changes in medications or other factors that may influence levels (C). Whole-blood trough levels are suitable for screening. Complete pharmacokinetic studies are more reliable than trough levels but are considered optional because of their expense and inconvenience. Single-point estimates of tacrolimus pharmacokinetics may also be more accurate than trough levels and may be a suitable alternative to complete pharmacokinetic studies (C).

mellitus at 1 yr to be substantially higher with tacrolimus (12 to 20%), compared with CsA (2 to 4%) (158–160). The odds ratio for posttransplant diabetes mellitus at 1 yr was 5.03 (95% confidence interval, 2.04 to 12.36) (162). In a more recent trial, the incidence of new-onset, posttransplant diabetes mellitus at 1 yr was 14.0% among patients treated with tacrolimus and azathioprine, 6.5% among patients treated with tacrolimus and mycophenolate mofetil (MMF), and 6.5% among patients treated with CsA and MMF (161). The incidence of hypercholesterolemia was higher among patients treated with CsA (14.5 to 31.9%), compared with tacrolimus (7.8 to 17.5%) (159,161). The incidence of tacrolimus nephrotoxicity was variable and dependent on the definition of toxicity (transient or sustained decreases in renal function, arteriopathy, or nonspecific tubulointerstitial atrophy and fibrosis), as well as the dose and target blood levels used (158–160,164–170). Small uncontrolled reports suggested that tacrolimus can be safely used for children (171).

Consequences. Failure to prevent acute rejection can lead to allograft failure. The role of acute and chronic tacrolimus nephrotoxicity in causing graft failure is unclear. However, the therapeutic window for tacrolimus is narrow, and the incidence of renal and nonrenal toxicity is roughly proportional to doses and blood levels.

Rationale. Whole-blood tacrolimus levels can be measured with a variety of analytical techniques (172–178). The bioavailability of tacrolimus is quite variable, being influenced by such factors as age, race, hepatic function, and concomitant medications (179–182). In addition, the range of blood levels at which tacrolimus is efficacious but not toxic appears to be very narrow. Therefore, it is generally not possible to determine the correct dose of tacrolimus for individual patients without measuring blood levels. Studies have demonstrated

that low tacrolimus blood levels are correlated with subsequent episodes of allograft rejection (161,164,168,169). High tacrolimus blood levels tend to be correlated with decreased renal allograft function (presumably as a result of nephrotoxicity) and other adverse effects (164,165,167–169,183). These correlations tend to confirm the biologically plausible notion that efficacy and toxicity are linked to drug exposure. However, the association between blood levels and tacrolimus efficacy and toxicity is inexact.

A number of factors affect tacrolimus blood levels. Like CsA, tacrolimus is metabolized by the cytochrome P-450 3A enzyme system. Therefore, as is the case with CsA, medications that inhibit or induce this enzyme pathway can increase or decrease tacrolimus levels, respectively (184). The intra- and interpatient variability in absorption and metabolism necessitates the use of blood levels for monitoring and adjustment of tacrolimus doses (178, 180,185,186). Although pharmacokinetic monitoring is likely more predictive of efficacy and toxicity than are trough level measurements, complete pharmacokinetic studies are inconvenient and expensive. Therefore, most transplant centers use trough tacrolimus levels for dose adjustments. Abbreviated (one- or two-point) area under the plasma concentration-time curve (AUC) determinations may be a reasonable alternative to trough level measurements or complete pharmacokinetic studies (187). There are few data to suggest how frequently levels need to be determined. However, levels should be measured more frequently during the first few months after transplantation. Levels should also be measured whenever there is a change in medications or other factors that may affect tacrolimus metabolism.

Efficacy and Toxicity of Sirolimus (Table 8)

Incidence. In a multicenter, randomized, open-label trial, 42 patients treated with CsA were compared with 41 patients treated with sirolimus (188). All patients received corticosteroids and azathioprine. The incidences of biopsy-confirmed acute rejection at 12 mo were similar for sirolimus (41%) and CsA (38%). Several adverse effects were significantly more common among patients treated with sirolimus *versus* CsA, including hypertriglyceridemia (51% *versus* 12%), hypercholesterolemia (44% *versus* 14%), thrombocytopenia (37% *versus* 0%), leukopenia (39% *versus* 14%), elevated alanine aminotransferase levels (17% *versus* 0%), and hypokalemia (34% *versus* 0%). Hyperglycemia was also more common (20% *versus* 7%), but this difference was not statistically significant, and the incidences of diabetes mellitus were the same for the two groups (1%). There were no statistically significant differences between sirolimus- and CsA-treated patients with respect to the incidences of CMV infection (14% *versus* 12%), hypertension (17% *versus* 33%), tremor (2% *versus* 14%), or gingival hyperplasia (0% *versus* 10%). Serum creatinine and uric acid levels were lower for patients treated with sirolimus, compared with CsA (188).

A similar efficacy and toxicity profile was demonstrated for sirolimus in a phase II trial ($n = 149$) (189). In that trial, sirolimus appeared to have a CsA-sparing effect, in that the rates of acute rejection among Caucasian patients treated with sirolimus were similar for patients treated with either full or reduced doses of CsA (189). However, sirolimus failed to reduce the rate of acute rejection among African American patients treated with a reduced dose CsA (189).

In another phase II, randomized, open-label trial, sirolimus ($n = 40$) was compared with CsA ($n = 38$) among patients who also received corticosteroids and MMF (190). At 12 mo, the incidences of biopsy-proven acute rejections were not significantly different for sirolimus (27.5%) and CsA (18.4%). Adverse effects that were significantly more frequent in the sirolimus-treated group included thrombocytopenia (45% *versus* 8%) and diarrhea (38% *versus* 11%). Increases in serum creatinine levels were significantly less common with sirolimus (18%), compared with CsA (39%). Tremor (5% *versus*

21%) and CMV viremia (5% *versus* 21%) were also significantly less common with sirolimus, compared with CsA (190). There were no differences in the incidences of hyperlipidemia, hyperglycemia, hyperuricemia, or hypertension (190).

Consequences. Sirolimus seems to be efficacious in preventing acute rejection when used in place of, or in combination with, CsA. However, most patients experience adverse effects.

Rationale. Methods that have been used to measure sirolimus blood levels include HPLC with ultraviolet light detection (188,191–194), HPLC-mass spectrometry (195), electrospray-HPLC-mass spectrometry (196), and immunophilin radioreceptor assays (197,198). Very few studies have been conducted to determine the relationship between blood levels of sirolimus and either acute rejection or toxicity. However, drug concentrations of sirolimus exhibit considerable intra- and interpatient variability, and monitoring therapy by measuring blood levels could be expected to improve efficacy and reduce toxicity. In a pilot, randomized, open-label, multicenter trial, steady-state whole-blood concentrations were used to adjust doses (188). Trough concentrations of “approximately 30 ng/ml” in the first 2 mo and 15 ng/ml thereafter were targeted (188). In a series of 150 patients who were monitored for 4 yr, trough levels of >15 ng/ml were correlated with hypertriglyceridemia, thrombocytopenia, and leukopenia, whereas levels of <5 ng/ml were associated with acute rejections (192). These and other preliminary data suggest that monitoring of sirolimus blood levels may be useful. Whether pharmacokinetic monitoring is superior to trough level measurements is unclear. In at least one study, trough levels were well correlated with AUC levels (192).

It is not yet clear whether sirolimus affects the pharmacokinetics of CsA (191,195,196,199), but blood levels of sirolimus were observed to be increased by CsA in at least one study (200). Sirolimus may cause modest increases in corticosteroid levels in patients receiving prednisone (201). Other preliminary studies suggested that blood levels of sirolimus vary with respect to race (black *versus* nonblack) but not gender (199). Dietary fat seems to increase sirolimus absorption (202). Very

Table 8. Efficacy and toxicity of sirolimus

Incidence	Although sirolimus is effective in preventing acute rejection, most patients experience at least some adverse effects.
Consequences	The relationship of sirolimus blood levels to efficacy and toxicity is not well defined. However, it is possible that inadequate therapeutic levels may lead to acute rejection, whereas very high levels may be more likely to cause adverse effects.
Rationale	It is possible that dose adjustment with the periodic measurement of blood levels could improve the efficacy and safety of sirolimus. However, very few studies have documented a relationship between sirolimus blood levels and acute rejection or adverse effects.
Recommendations	Evidence of toxicity should be sought during periodic history assessments and physical examinations (A). Lipoprotein levels, complete blood counts, and platelet levels should be measured periodically (B). The role of therapeutic monitoring with blood levels and/or pharmacokinetic studies has not yet been determined (C).

few studies have evaluated the potential utility of pharmacodynamic monitoring of sirolimus (203).

Efficacy and Toxicity of MMF (Table 9)

Screening tests. White blood cell counts and hemoglobin levels (or hematocrit values) may be used to detect leukopenia and/or anemia. Clinical manifestations of nonimmune toxicities of MMF are usually detectable in routine history assessments and physical examinations.

Incidence. The recommended starting dose of MMF is 1.0 g twice daily for adults. The dose for children is 600 mg/m² twice daily (204). The authors of one study recommended that the dose for children should be 600 mg/m² twice daily when MMF is used in combination with CsA, 300 mg/m² twice daily when MMF is used with tacrolimus, and 500 mg/m² twice daily when MMF is used without a calcineurin inhibitor (205). Capsules, liquid, and intravenous preparations are available. Higher doses are associated with increased toxicity but little added efficacy (206–210), except perhaps for blacks. The incidence of clinical adverse reactions to MMF seems to be high. However, most of the large, randomized, controlled trials compared MMF with azathioprine rather than placebo, making it difficult to determine the true incidence of adverse effects attributable to MMF (207–210). The principle nonimmune toxicities of MMF are gastrointestinal and hematologic. At the 2 g/d dose, diarrhea was reported in 13% (206), 28% (208), and 35% (210) of cases in three large, randomized, controlled trials. In these trials, with 2 g/d MMF, abdominal pain occurred in 12% (206), 26% (208), and 30% (210) of cases, respectively. Vomiting occurred in 2% (206), 12% (208), and 16% (210), leukopenia occurred in 11% (206), 19% (208), and 20% (210), anemia occurred in 4% (206), 15% (208), and 16% (210), and thrombocytopenia occurred in 4.2% (206), 9% (208), and 8.8% (210) of cases, respectively. The principal short-term, nonspecific, immune-related toxicity was an increased incidence of infection. For example, at the dose of 2 g/d, CMV infection occurred in 12 to 16% of cases (206–208,210). In a case-control study, the severity of CMV infection was higher with

MMF, compared with azathioprine (211). Similarly, the initiation of MMF administration was associated with an increase in hepatitis C virus (HCV) viremia (212).

Consequences. Although MMF seems to be efficacious in preventing acute rejection, many patients experience adverse effects. Treatment of gastrointestinal, hematologic, or other adverse effects is generally with dose reductions, dosing interval changes, or discontinuation of MMF administration. For example, in one large, randomized controlled trial, the 2 g/d dose of MMF was reduced because of leukopenia in 15% of cases and MMF administration was discontinued because of leukopenia in 2 to 3% of cases (208).

Rationale. Techniques for determining mycophenolic acid (MPA) blood concentrations seem to be reliable (213–216). MMF is a prodrug that is highly bioavailable, with 94% absorption after an oral dose (217). MMF is rapidly hydrolyzed to MPA, the active compound, which then undergoes enterohepatic recirculation (218,219). This latter property may complicate the interpretation of trough blood levels. MPA is highly protein-bound (214), and levels of MPA are correlated with serum albumin levels (219). MPA is metabolized to MPA glucuronide (MPAG). Although MPAG is not thought to have pharmacologic activity, it may contribute to toxicity. Because MPAG is renally excreted, patients with reduced renal function may have high levels of MPAG; this may help explain an increased incidence of gastrointestinal toxicity among patients with reduced renal function (220).

Pharmacokinetic studies of MPA demonstrated substantial intra- and interindividual variations for both adults and children (218,219,221–224). Levels in children may be higher than levels in adults treated with a comparable dose (600 mg/m² twice daily) (224). The total AUC values for MPA were similar with oral or intravenous administration, with intraindividual and interindividual coefficients of variation of 25% and 10%, respectively (218). A number of factors affect MPA levels. The maximal concentration of MPA and the AUC value determined immediately after transplantation were only 30 to 50% of those measured for patients 3 mo after transplantation (218,222).

Table 9. Efficacy and toxicity of MMF^a

Incidence	Although MMF is effective in preventing acute rejection, most patients experience at least some adverse effects.
Consequences	Some adverse effects of MMF, <i>e.g.</i> , bone marrow suppression, are potentially fatal.
Rationale	The high incidence of serious adverse effects that respond to dose reductions or withdrawal of MMF warrants close surveillance.
Recommendations	Evidence of toxicity should be sought during periodic history assessments and physical examinations (B). Hemoglobin levels, hematocrit values, and white blood cell counts should be measured at least weekly for months 1 to 2, every 2 wk for months 3 to 4, monthly for months 4 to 12, and then every 3 to 6 mo (B). Platelet counts should be measured at least every 2 wk for months 1 to 2, monthly for months 3 to 4, every 3 to 4 mo until the end of the first 1 yr, and then yearly (B). Indirect evidence suggests that therapeutic blood level monitoring may help improve efficacy and reduce toxicity (B).

^a MMF, mycophenolate mofetil.

However, free levels remained unchanged, suggesting that the increase in MPA levels was largely attributable to increased levels of MPA bound to plasma proteins (222). The pharmacologic activity of MMF is thought to be correlated with free and not bound MPA levels. Therefore, reductions in plasma protein levels (as may occur in liver disease, for example) may increase the free levels of MPA without altering whole-blood concentrations. The MPA maximal concentration and AUC may be reduced by concomitant administration of antacids containing magnesium and aluminum (225) and by cholestyramine (218). Tacrolimus seems to increase MPA levels (181,205,226). However, in most (205,227) but not all studies (228), CsA reduced the blood concentrations of MPA.

The variability in MPA levels suggests that measurements of plasma MPA levels could be beneficial. Indeed, blood levels of MPA have been demonstrated to correlate with the incidence of acute rejection in adults and children (204,213,223,229). A recent, blinded, randomized trial demonstrated that targeting of different MPA AUC values resulted in different incidences of acute rejection and toxicity (230). MPA trough levels have also been found to be correlated with hemoglobin levels (231). It has been suggested that MMF levels should be monitored in children when MMF is used as rescue therapy after acute rejection (232). Although the case for monitoring of MMF blood levels seems to be compelling, additional data are needed to establish whether monitoring will improve outcomes.

Monitoring the pharmacodynamic activity of MMF, by monitoring the activity of the enzyme inosine monophosphate dehydrogenase, which is inhibited by MPA, has also been suggested as a potential method to monitor the efficacy of MMF and adjust its dose (233). Because this is a key enzyme in the *de novo* biosynthesis of purines, measurement of its activity could be used to effectively measure the desired pharmacodynamic effect of MMF, thereby offering a rational approach to the monitoring of MMF therapy (233,234). Additional studies are needed to determine whether pharmacodynamic monitoring improves outcomes.

Efficacy and Toxicity of Azathioprine (Table 10)

Incidence. There have been few randomized controlled trials demonstrating the efficacy of azathioprine, but indirect evidence suggests that azathioprine reduces the incidence of acute rejection (235,236). Leukopenia occurs in approximately 35% of renal transplant cases when initial azathioprine doses are at least 3 mg/kg daily, but white blood cell counts are usually not lower than 2500/ μ l (237). When azathioprine doses are initiated at 1 to 2 mg/kg per d, leukopenia occurs in approximately 10 to 25% of cases (237,238). The presence or absence of a spleen influences the incidence of leukopenia (238). Thrombocytopenia occurs in approximately 13% of cases and, although macrocytic blood cells are a common finding (239,240), anemia is not frequent. Hepatotoxicity, including rare cases of veno-occlusive disease, occurs in a small percentage of patients, most commonly in the first 6 mo after transplantation (241,242). Gastrointestinal toxicity (usually nausea and vomiting) occurs in approximately 10% of cases, but rare patients develop severe gastrointestinal hypersensitivity, which mimics infectious gastroenteritis (243,244).

Consequences. Hematologic and gastrointestinal toxicities are usually dose-related and respond to dose reductions (245). However, the gastrointestinal hypersensitivity reaction or hepatic veno-occlusive disease usually necessitates the withdrawal of azathioprine. Some early uncontrolled reports linked azathioprine use with pancreatitis in renal transplant recipients, but this association was not confirmed in a randomized controlled trial (246).

Rationale. Azathioprine is metabolized to 6-mercaptopurine. The metabolites of azathioprine can be readily measured by HPLC (247). The bioavailability of azathioprine is low and highly variable (range, 5 to 24%) (248). Both azathioprine and 6-mercaptopurine are rapidly cleared, so that blood levels are low and would not be expected to be correlated with clinical efficacy or toxicity (249). The final metabolic end products, *i.e.*, 6-thioguanine nucleotides, are cleared very slowly (249).

Table 10. Efficacy and toxicity of azathioprine

Incidence	Although azathioprine is effective in preventing acute rejection, many patients experience adverse effects.
Consequences	Some of the adverse effects of azathioprine, <i>e.g.</i> , bone marrow suppression, are potentially fatal.
Rationale	The high incidence of serious adverse effects that respond to dose reductions or withdrawal of azathioprine warrants close surveillance.
Recommendations	Evidence of toxicity should be sought during periodic history assessments and physical examinations (B). Hemoglobin levels, hematocrit values, and white blood cell counts should be measured at least weekly for months 1 to 2, every 2 wk for months 3 to 4, monthly for months 4 to 12, and then every 3 to 6 mo (B). Platelet counts should be measured at least every 2 wk for months 1 to 2, monthly for months 3 to 4, every 3 to 4 mo until the end of the first 1 yr, and then yearly (B). Alanine aminotransferase, aspartate aminotransferase, and total bilirubin levels should be measured at least monthly for the first 3 mo, every 3 to 4 mo until the end of the first 1 yr, and then annually (C). There is insufficient evidence for or against monitoring of blood levels or pharmacodynamic effects to enhance efficacy or reduce toxicity (C).

The dose of azathioprine is correlated with levels of 6-thioguanine (250). Interestingly, 6-thioguanine nucleotides appear to be concentrated in granulocytes, which suggests that these metabolites could be important in the myelotoxicity of azathioprine (251). In some cross-sectional studies, leukopenia has been observed to be correlated with 6-thioguanine levels (250,252). In one prospective study, 360 patients were randomized to receive high doses of azathioprine (monitored and adjusted on the basis of 6-thioguanine levels) and were compared with patients treated with lower doses of azathioprine (253). Acute rejection episodes were less frequent for the high-dose, monitored group, but leukopenia was also more common. Unfortunately, the trial design did not permit the authors to determine the role of therapeutic monitoring (compared with the higher dose of azathioprine) in altering the efficacy or toxicity of azathioprine (253).

Thiopurine methyltransferase is an important enzyme in the metabolism of 6-thioguanine nucleotides, and this enzyme exhibits considerable genetic variability in the general population (254,255). In theory, individuals with very low levels of this enzyme may be susceptible to myelotoxicity because of high levels of 6-guanine nucleotides, and individuals with low levels may be more susceptible to acute rejection (255–257). Therefore, measurements of the activity of this enzyme could theoretically predict the efficacy and toxicity of azathioprine. Thiopurine methyltransferase activity increases after transplantation in some patients, and in some studies the incidence of acute rejection was inversely correlated with the increase in thiopurine methyltransferase activity (255,258). In another study, however, the authors failed to observe the predicted correlation between baseline thiopurine methyltransferase activity and 6-thioguanine levels, and neither enzyme activity nor substrate levels predicted the incidence of acute rejection among 82 patients (259). Negative results were also reported by others (260). Therefore, there is currently insufficient evidence to suggest that therapeutic drug monitoring would improve the efficacy or toxicity of azathioprine.

Monitoring hematologic toxicity using blood counts, monitoring hepatic toxicity using liver enzyme and serum bilirubin levels (261), and assessing other toxicities using clinical symptoms are the only practical means for minimizing azathioprine toxicity. Because myelosuppression can occur with azathioprine at any time after transplantation, monitoring of white blood cell counts must be continued throughout the course of treatment. Allopurinol can alter azathioprine metabolism and thereby cause life-threatening bone marrow suppression, and it is generally best to avoid using allopurinol and azathioprine in combination unless it is absolutely necessary. If allopurinol is used for azathioprine-treated patients, the dose of azathioprine should be reduced. The amount of dose reduction may be dictated by the dose of allopurinol. Thus, the dose of azathioprine may need to be drastically reduced, *e.g.*, to 25 mg/d, when the dose of allopurinol is 300 mg/d, whereas less marked reductions of the azathioprine dose may be appropriate when the dose of allopurinol is 100 mg/d. Co-trimoxazole has been reported to cause leukopenia in azathioprine-treated patients (257,262). Despite newer drug regimens, it seems likely that azathioprine will continue to be used for many years for patients with successful grafts who are already receiving azathioprine, for patients who are intolerant of other agents, for some patients because of economic reasons, and for pregnant patients.

Efficacy and Toxicity of Corticosteroids (Table 11)

Incidence. Clinical signs of corticosteroid toxicity, which are observed relatively soon after the initiation of prednisone treatment, include cushingoid facial and body habitus changes, changes in mood or mentation, acne and other skin changes, hypertension, peptic ulcer disease, and myopathy. Bone and eye toxicities generally occur later. Avascular necrosis of the hips exhibits a peak incidence toward the end of the first year and in the second year after transplantation, whereas osteoporosis, cataracts, glaucoma, and growth retardation of children can occur even later.

Table 11. Efficacy and toxicity of corticosteroids

Incidence	Although corticosteroids are effective in preventing acute rejection, most patients experience at least some adverse effects.
Consequences	Inadequate corticosteroid doses may cause acute rejection, which may in turn lead to chronic allograft nephropathy. However, corticosteroids cause acute and chronic toxicity, particularly when used in high doses.
Rationale	The high incidence of adverse effects and the availability of palliative therapies justify routine monitoring for many steroid-related complications.
Recommendations	Evidence of toxicity should be sought during periodic history assessments and physical examinations (A). The growth of children should be closely monitored (B). BP, lipoprotein levels, and blood glucose levels should be measured periodically (B). Ophthalmologic examinations should be performed annually (B). Lumbar spine and hip bone mineral densities should be assessed by dual x-ray absorptiometry (C). There is insufficient evidence for or against the use of pharmacokinetic and/or pharmacodynamic monitoring to improve efficacy and reduce toxicity (C).

The incidence of many steroid-induced complications is influenced by the concomitant use of other immunosuppressive agents, such as CsA and tacrolimus. The overall incidence of hypertension among prednisone-treated renal transplant recipients is 75 to 85% (263–271). Hypercholesterolemia occurs by 3 to 12 mo in 38 to 68% of patients treated with prednisone and CsA (264,267,269,272,273). The incidence of hypercholesterolemia may be as low as 13% among patients in stable condition for whom the dose of prednisone can be reduced to ≤ 10 mg/d in the late posttransplant period (272). Hypercholesterolemia was observed for only 7 to 30% of patients treated with tacrolimus and prednisone (273,274). Hypertriglyceridemia is less common than hypercholesterolemia and occurs in 15 to 35% of patients treated with prednisone and CsA (264,272). HDL cholesterol levels are generally normal in prednisone-treated renal transplant recipients and decrease as the dose of prednisone is reduced.

The incidence of new-onset diabetes mellitus is affected both by the prednisone dose and by the concomitant diabetogenic effects of CsA (159,275,276) or tacrolimus (159,277–279). The overall incidence of new-onset diabetes mellitus among renal transplant recipients treated with prednisone and CsA, with or without azathioprine, is generally reported to be 3 to 17% (263,265,266,269,270,275,280–282), with black (283), older (282), and more obese (282) patients experiencing higher incidences of posttransplant diabetes mellitus. The incidence of new-onset diabetes mellitus among tacrolimus-treated renal transplant recipients has been reported to be higher than that among CsA-treated patients, ranging from 10 to 20% (159,284,285).

Bone complications are common among prednisone-treated patients, and bone mineral density is influenced by many factors (286). Avascular necrosis, however, occurs in only 1.1 to 5.5% of cases (263,266,269,270). The incidence of symptomatic cataracts has been reported to be 9 to 21% (265,269,270). As detected in annual systematic screening, cataracts occurred in 21 of 38 patients (53%) treated with high doses of corticosteroids, 33 of 117 patients (28%) treated with low doses of steroids, and 1 of 16 patients (6%) who received no steroids (287).

The growth of children is adversely affected by the daily administration of corticosteroids, even in very small doses. The onset of puberty is also delayed in children who receive corticosteroids, further delaying growth. Growth rates are higher for children who receive corticosteroids on an alternate-day schedule (288–290), but $< 30\%$ of children are receiving alternate-day prednisone treatments by 4 yr after transplantation (4).

It is difficult to accurately assess the incidence of adverse effects caused by corticosteroids, because most renal transplant recipients receive at least some corticosteroid therapy. However, several randomized, controlled, steroid-withdrawal trials compared the incidences of adverse effects (263–269). Patients in the withdrawal arms of these trials usually received steroids early after transplantation, and many who experienced failure of withdrawal attempts were returned to steroid therapy. Nevertheless, these trials provide a clearer view of the incidence of

adverse effects attributable to long-term corticosteroid use. Differences in the incidences of hypertension (variously defined) were generally small, *e.g.*, 2 to 6% lower in the withdrawal groups (265–267). Hypercholesterolemia was 10 to 38% lower in the withdrawal groups (264,267,269); however, HDL cholesterol levels were proportionately reduced. The incidence of diabetes mellitus was 2 to 10% lower in the withdrawal groups (263,265–267,269). Cataracts were 10 to 20% less frequent in the withdrawal groups (265,269), and the incidence of avascular necrosis was 0.1 to 3.0% lower in the corticosteroid withdrawal groups (263,266,269). The best growth rates for children are observed for those from whom corticosteroids have been withdrawn; these children frequently grow at a normal rate (291,292).

A systematic review of controlled and uncontrolled trials examined the adverse effects of steroids in steroid withdrawal or steroid avoidance CsA-based immunosuppressive regimens (293). Included were 10 trials that examined either hypertension, diabetes mellitus, fractures, avascular necrosis of the hips, or cataracts (263–266,269,286,287,294–296). The estimated incidences of late, steroid-related, side effects were as follows: hypertension, 15%; diabetes mellitus, 10%; fractures, 2%/yr; avascular necrosis of the hip, 8%; cataracts, 22% (293).

Consequences. A number of randomized controlled trials (263–269,297–300) and a meta-analysis (301) have examined the feasibility of prednisone withdrawal or avoidance after renal transplantation. However, in most of those trials the incidence of acute rejection was increased in the steroid withdrawal/avoidance group, and in at least one large study graft survival was also reduced in long-term follow-up monitoring (266). In uncontrolled trials involving children, approximately 50% of patients underwent prednisone withdrawal without immediate acute rejection, but for almost 50% of that group steroid administration was reinitiated because of late rejections (302,303). As a result, the long-term use of corticosteroids continues to be a mainstay of immunosuppression for both children and adults. Whether newer immunosuppressive agents, such as tacrolimus or MMF, could allow prednisone to be withdrawn is being actively investigated. It is currently necessary to monitor the adverse effects of corticosteroid therapy.

Rationale. Blood levels of prednisone and its major metabolite prednisolone can be measured with HPLC. Endogenous cortisol levels, which can also be measured with HPLC, may reflect the degree of adrenal suppression. However, the biologic effects of the adrenal corticosteroids are diverse, and no laboratory measurements have been proven to be reliable in monitoring either efficacy or toxicity. Prednisone and methylprednisolone pharmacokinetics exhibit considerable inter- and intraindividual variability (304–309). The bioavailabilities of prednisone and prednisolone exceed 85% (310). Clearance tends to decrease with time after transplantation (307). Clearance also varies with race. Black subjects exhibit lower methylprednisolone clearance rates, compared with white subjects, and this may predispose black patients to a higher incidence of steroid-related side effects, such as diabetes mellitus (311,312). The metabolic clearance of prednisone is inhibited by CsA

(313), oral contraceptives (314,315), and ketoconazole (316,317). Indeed, ketoconazole has been demonstrated to cause increased weight gain and more bone loss among prednisone-treated patients (318). Conversely, the clearance of prednisone may be increased by the concomitant use of drugs such as phenytoin, phenobarbital, or rifampin (319).

There are virtually no studies correlating the rate of acute or chronic allograft nephropathy with pharmacokinetic or pharmacodynamic parameters for corticosteroids. A few studies attempted to correlate pharmacokinetic parameters with the adverse effects of steroids. However, the results of those studies were variable. For example, some (320,321), but not all investigators (322) were able to correlate the development of cushingoid features with differences in prednisone pharmacokinetic parameters. Other investigators also attempted to use cortisol levels as a pharmacodynamic measure of corticosteroid activity. In one study, for example, it was demonstrated that the degree of cortisol suppression by methylprednisolone was greater in older men, compared with younger men, and this greater age-related cortisol suppression was correlated with a greater methylprednisolone AUC value (323). As is the case for prednisone and prednisolone pharmacokinetics, there is considerable variability in the pharmacodynamic responses to exogenous steroids, as measured by cortisol levels (324). It has been suggested that single timed measurements of prednisone blood levels could be used to guide therapy (305,306), but there are no clinical data to suggest that these measurements would reliably predict efficacy or toxicity.

IV. Cardiovascular Disease

Cardiovascular Disease (Table 12)

Definition. CVD is defined as ischemic heart disease, cerebral vascular disease, or peripheral vascular disease.

Incidence. In one study, the prevalence of ischemic heart disease (detected by routine clinical measures) was 9.5% at the time of transplantation (325). The incidence of new ischemic heart disease events in 46 ± 36 mo of follow-up monitoring after transplantation was 11.1% among patients without histo-

ries of prior ischemic heart disease and 15.1% among all patients. The prevalence of cerebral vascular disease was 3.7% at the time of transplantation. The incidence of cerebral vascular disease events was 6.0% among patients without prior cerebral vascular disease and 7.3% among all patients. The prevalence of all CVD types at the time of transplantation was 12.9%. The incidence of new events was 15.8% among patients without prior CVD and 21.3% among all patients, with or without prior CVD (325). The incidence of CVD was approximately fivefold greater than predicted from Framingham Heart Study data for patients of comparable age and gender (325). In a more recent study, the cumulative (actuarial) incidence of primary and secondary ischemic heart disease events was 23% by 15 yr after transplantation (326). The cumulative incidence of cerebral vascular disease was 15% by 15 yr. The cumulative incidence of peripheral vascular disease was also 15% by 15 yr after transplantation (326). In another cross-sectional study ($n = 406$), the incidence of ischemic heart disease was 14% (24% for diabetic patients and 12% for nondiabetic patients), that of cerebral vascular disease was 3%, and that of peripheral vascular disease was 4% (327). Compared with the general population, odds ratios for angina pectoris were 12 and 16 for men and women 40 to 49 yr of age, 6 and 4 for men and women 50 to 59 yr of age, and 3 and 4 for men and women 60 to 69 yr of age, respectively (327). Similar data have been reported by others (325,326,328–333).

Consequences. CVD is a major cause of morbidity and death among renal transplant recipients (334,335). Recently, the National Kidney Foundation convened a task force on CVD and reviewed the available evidence linking risk factors to CVD in patients with renal disease, including renal transplant recipients (336). The task force concluded that renal transplant recipients were at high risk for CVD and that a number of potentially modifiable risk factors could be targeted for intervention (336).

Rationale. There are two possible reasons to screen for CVD, *i.e.*, (1) detection of symptomatic CVD could lead to the relief of symptoms, and (2) detection of asymptomatic disease

Table 12. Cardiovascular disease^a

Incidence	Approximately 23% of patients develop ischemic heart disease, 15% cerebral vascular disease and 15% peripheral vascular disease by 15 yr after transplantation.
Consequences	Morbidity resulting from ischemic heart disease, stroke, or peripheral arterial disease, premature death, or allograft loss (death with a functioning graft) may occur.
Rationale	The high incidence and severe complications warrant aggressive screening and intervention, with risk factor modification.
Recommendations	CVD risk should be assessed during periodic routine history assessments and physical examinations (A). Multiple risk factor interventions should be aggressively pursued (A). There is insufficient evidence to suggest that screening of asymptomatic patients with electrocardiograms or cardiac stress tests reduces morbidity or mortality rates after renal transplantation (C). There is insufficient evidence to suggest that screening of asymptomatic patients with carotid artery ultrasonography reduces morbidity or mortality rates after renal transplantation (C).

^a CVD, cardiovascular disease.

could lead to the prevention of CVD-related morbidity and death. Routine history assessments and physical examinations seem to be appropriate tools for detecting symptomatic CVD for the relief of symptoms; however, the sensitivity and specificity of routine history assessments and physical examinations to detect CVD have never been rigorously studied.

Few studies have defined the sensitivity and specificity of screening tests for ischemic heart disease in renal transplant recipients. However, studies of the general population suggest that the sensitivity and specificity of exercise electrocardiography (ECG), exercise thallium testing, dipyridamole thallium (or sestamibi) testing, adenosine thallium (or sestamibi) testing, exercise echocardiography, dobutamine echocardiography, and dipyridamole echocardiography are roughly 70 to 80% and 85 to 95%, respectively. Therefore, these tests exhibit only fair sensitivity and specificity. A number of new tests have recently been developed to detect coronary atherosclerosis, *e.g.*, magnetic resonance imaging (MRI), electron-beam computed tomography (CT), and contrast-enhanced CT. However, inadequate data are available to allow the recommendation of any of these newer tests for the screening of renal transplant recipients. In general, the positive and negative predictive values of a particular screening test are dependent on the underlying prevalence of the disease. Therefore, the high prevalence of ischemic heart disease after renal transplantation should theoretically increase the predictive value of screening tests for transplant recipients, compared with the general population. However, these predictive values may still be too low to make screening tests cost-effective in many cases. The United States Preventive Services Task Force concluded that there is insufficient evidence to recommend for or against screening middle-age and older men and women for asymptomatic coronary artery disease with resting ECG, ambulatory ECG, or exercise ECG (category C evidence) (337).

Even fewer studies are available for assessment of the utility of screening tests for cerebral vascular disease and peripheral vascular disease after renal transplantation. Possible screening tests for cerebral vascular disease include carotid artery auscultation during physical examinations, as well as Doppler flow and ultrasonographic examinations of the carotid arteries. The United States Preventive Services Task Force concluded that there is insufficient evidence to recommend for or against screening asymptomatic individuals for carotid artery stenosis, using physical examinations or carotid artery ultrasonography (category C evidence) (338). However, they suggested that a recommendation could be made on the basis of other grounds for high-risk patients, provided that the quality of available vascular surgical care was high. Possible screening methods for peripheral vascular disease could include history assessments and physical examinations, segmental arterial BP determinations (usually using Doppler ultrasonography), and cutaneous oxygen saturation testing. However, the role, if any, for screening of asymptomatic transplant recipients with any of these tests is unclear. The United States Preventive Services Task Force recommended against screening for peripheral vascular disease in asymptomatic patients in the general population (category D evidence) (339).

Pretransplant CVD is an important risk factor for CVD after renal transplantation (326,340). Therefore, CVD screening should be part of the pretransplant evaluation. Pretransplant screening for CVD has been covered in other guidelines (1). Any CVD screening strategy for the posttransplant period should take into account the results of pretransplant screening. For example, patients who have already been identified as being at high risk for posttransplant CVD, as a result of positive pretransplant screening, may benefit from additional periodic screening after transplantation more than do patients who exhibited negative pretransplant screening results.

Preoperative Screening for CVD (Table 13)

Definition. CVD was defined as ischemic heart disease, cerebral vascular disease, or peripheral vascular disease.

Consequences. The risk for ischemic heart disease events and stroke is increased by surgery. Because the risk for CVD is high among renal transplant recipients, it is likely that the risk of surgery for renal transplant recipients is even greater than that for the general population.

Rationale. Guidelines have been developed by the American College of Physicians for assessment and management of the perioperative risk for coronary artery disease (341,342). These guidelines are generally applicable to renal transplant recipients who are being considered for surgery. The guidelines classify patients as having low, intermediate, or high risk, on the basis of a modified cardiac risk index. The cardiac risk index assigns points as follows: myocardial infarction <6 mo earlier, 10; myocardial infarction >6 mo earlier, 5; angina with walking one to two level blocks or climbing one flight of stairs or less at a normal pace, 10; inability to perform any physical activity without developing angina, 20; alveolar pulmonary edema within 1 wk, 10; alveolar pulmonary edema ever, 5; suspected critical aortic stenosis, 20; ECG rhythm other than sinus or sinus plus atrial premature beats, 5; more than five premature ventricular contractions, 5; P_{O_2} of <60 mmHg, P_{CO_2} of >50 mmHg, potassium level of <3 mM, blood urea nitrogen level of >50 mM, serum creatinine level of >260 μ M, or bedridden, 5; age >70 yr, 5; emergency surgery, 10. The points are added and classes are assigned as follows: class I, 0 to 15 points; class II, 20 to 30 points; class III, >30 points.

Class II or III in the modified cardiac risk index system predicts a high risk for perioperative cardiac events (10 to 15%). Low cardiac risk index scores (class I) do not reliably identify patients who have low risks for perioperative cardiac events, and additional information on “low-risk” variables should be collected for these patients. Low risk (<3%) is predicted by the presence of no cardiac risk factors or one cardiac risk factor, as defined by the low-risk variables. These risk factors include age of >70 yr, history of angina, diabetes mellitus, Q waves in electrocardiograms, history of myocardial infarction or ventricular ectopy, ST-segment ischemic abnormalities during resting ECG, hypertension with severe left ventricular hypertrophy, and history of congestive heart failure.

Low-risk patients may proceed directly to surgery without further testing. For patients who are at intermediate risk, con-

Table 13. Preoperative screening for CVD

Incidence	The incidence of CVD events after surgery among renal transplant recipients is unknown, but it is likely to be at least as high as that in the general population.
Consequences	The risk for perioperative coronary events, especially with vascular surgery, is probably high among renal transplant recipients.
Rationale	Adequate assessment of the risk for perioperative coronary events allows measures to be taken to reduce that risk. Measures that may help prevent perioperative morbidity and death include prior coronary revascularization and perioperative management with pulmonary artery catheterization.
Recommendations	<p>Preoperative coronary disease risks should be assessed, and patients can be classified as being at low, intermediate, or high risk according to the modified cardiac risk index (A).</p> <ul style="list-style-type: none"> ● low-risk patients may proceed to surgery without further evaluation (B). ● intermediate-risk patients undergoing vascular surgery should undergo dipyridamole thallium (or sestamibi) or dobutamine echocardiography (B). ● intermediate-risk patients undergoing nonvascular surgery should undergo dipyridamole thallium (or sestamibi) or dobutamine echocardiography (C). ● High-risk patients should be considered for revascularization before the planned surgery if the need for surgery is not urgent (C). <p>Some high-risk patients may benefit from perioperative management using a pulmonary artery catheter (B).</p> <p>Elective surgery should probably be postponed for patients who have experienced strokes or transient ischemic attacks in the previous 6 mo (B).</p> <p>There are insufficient data to determine whether identification of individuals with asymptomatic carotid artery disease should be part of the presurgical evaluation (C).</p>

sideration should be given to noninvasive cardiac stress testing. Exercise testing is not suitable for many transplant recipients and has not reliably predicted patients at high risk for surgery. Dipyridamole thallium (or sestamibi) imaging and dobutamine stress echocardiography provide useful stratification information for intermediate-risk patients undergoing vascular surgery, especially if the test results are normal. For patients undergoing nonvascular surgery, neither dipyridamole thallium imaging nor dobutamine echocardiography reliably predicts adverse perioperative cardiac events, as indicated in studies of the general population. However, because the probability of CVD is high after renal transplantation, it is possible that these tests are more reliable for renal transplant recipients than for the general population.

Asymptomatic patients who have recently undergone coronary angiography can be considered at low risk and can proceed with surgery. Patients with unstable angina should undergo cardiac catheterization and should be treated according to usual clinical standards. For high-risk patients who are not candidates for revascularization, consideration should be given to canceling, or at least postponing, surgery if the risk posed by not proceeding with surgery is lower than the perceived cardiac risk. The role of coronary revascularization in preventing perioperative coronary events has not been adequately studied. In deciding whether intermediate- or high-risk patients should undergo revascularization, the risk of angiography and the risk of the revascularization procedure(s) should be taken into account. Of course, if revascularization is clinically indicated on the basis of probable long-term outcomes, then this may best be

performed before the planned surgery, if the condition of the patient allows this approach to be taken. Finally, studies have suggested that perioperative monitoring with a pulmonary artery catheter may be useful for some patients.

There are virtually no data on the risk of noncardiac vascular disease events among patients in the general population who undergo noncardiac surgery. Therefore, screening for asymptomatic carotid artery disease as part of preoperative assessments is probably not warranted. If possible, elective surgery should be postponed for patients who have experienced a stroke or transient ischemic attack within the previous 6 mo. Such patients should be evaluated with carotid artery ultrasonography, and guidelines for the management of carotid artery disease have been developed by the American Heart Association (343,344). Several studies, but no randomized controlled trials, have addressed the risk of noncardiac vascular disease complications in the perioperative period for cardiac surgery. Identified risk factors include a previous stroke, the presence of carotid artery bruit, a history of hypertension, advanced age, diabetes mellitus, and the severity of carotid artery stenosis in ultrasonograms (345–347). Some investigators have advocated simultaneous carotid endarterectomy and coronary artery bypass grafting (348–352), whereas others have advocated a more conservative approach (353,354). The American Heart Association guidelines categorize simultaneous bypass grafting and endarterectomy as an uncertain indication (344). In the absence of data, it is reasonable to follow the approach suggested in the American Heart Association guidelines.

Aspirin Prophylaxis for CVD (Table 14)

Prophylaxis. Aspirin is safe. It is an effective antiplatelet agent, and it is inexpensive.

Rationale. The effectiveness of aspirin prophylaxis in preventing CVD has been extensively studied in nontransplant patients. Long-term aspirin use has been demonstrated to reduce CVD events and overall mortality rates among patients with histories of myocardial infarction, stroke, or transient ischemic attacks or other evidence of CVD (355). On the strength of the evidence, a number of guidelines have recommended the prophylactic use of aspirin for patients with CVD (355–359). A low dose of aspirin (75 mg) appears to be as effective as higher doses (355,360). Other antiplatelet drugs do not appear to be more beneficial than aspirin (355). Aspirin may increase the risk of hemorrhagic stroke, but the reduction in myocardial infarction and ischemic stroke rates appears to outweigh this risk for the general population (355,361).

Some studies indicate that aspirin may also be effective as primary prevention, *i.e.*, when used for patients without known CVD (355). However, the strength of the evidence for the use of aspirin for patients without CVD is less certain. The United States Preventive Services Task Force concluded that there was no evidence for or against the use of aspirin for primary prevention (362). The American Diabetes Association recommends the use of aspirin for type I and type II diabetic patients who have additional risk factors for CVD (358).

Hypertension (Table 15)

Definition. For adults ≥ 18 yr of age who are not taking antihypertensive medications, BP values of ≥ 140 mmHg (systolic) or ≥ 90 mmHg (diastolic) (based on the average of two or more readings) are considered hypertension. BP values of < 120 mmHg (systolic) and < 80 mmHg (diastolic) are considered to be optimal (363).

Incidence. The prevalence of hypertension varies with the type of immunosuppressive medications, the time after transplantation, and other factors. Among patients treated with prednisone and azathioprine, the prevalence of hypertension (variously defined) was 53% (364), 42% (365), 60% (366), and 72% (367) at 1 yr, 38% (365) and 58% (368) at 2 yr, and 46% (364), 58% (366), and 71% (367) at 5 yr after transplantation. Among patients treated with CsA, the prevalence of hypertension was 63% (365), 64% (367), 66% (369), 71% (366), and 78% (370) at 1 yr, 61% (365) and 73% (355) at 2 yr, 77% (371) at a mean of 3.75 yr, and 70% (366), 83% (367), and 85% (369) at 5 yr. Among 29,751 cadaveric transplant recipients at 1 yr, 44.5% were normotensive (systolic BP of < 140 mmHg), 37.4% exhibited systolic BP of 140 to 159 mmHg, 13.9%

exhibited systolic BP of 160 to 179 mmHg, and 4.2% exhibited systolic BP of ≥ 180 mmHg. Among 14,351 cadaveric transplant recipients at 5 yr, 46.1% were normotensive (systolic BP of < 140 mmHg), 37.5% exhibited systolic BP of 140 to 159 mmHg, 12.7% exhibited systolic BP of 170 to 179 mmHg, and 3.7% exhibited systolic BP of ≥ 180 mmHg (372). Among children, the prevalence of hypertension (defined as the use of antihypertensive medication) was 79% at 1 mo after transplantation; the prevalence decreased to 59% at 24 mo (373).

Common causes of posttransplant hypertension include (1) allograft dysfunction resulting from acute rejection or chronic allograft nephropathy, (2) treatment with corticosteroids or calcineurin inhibitors, (3) diseased native kidneys, (4) renal artery stenosis, and (5) essential hypertension (364,374). The incidence of radiographically evident renal artery stenosis varies substantially and depends on which patients are selected for screening. Among adult transplant recipients, the incidence of renal artery stenosis was 2.0 to 6.6% in most studies (375–378). In one study in which angiography was routinely performed for hypertensive patients, the incidence was 11.6% (379). The incidence may be higher among cadaveric *versus* living donor transplants (375). Among children, the incidence has been reported to be as high as 15% (375,380).

Consequences. Many studies in the general population have demonstrated that hypertension causes CVD and that its detection and treatment can reduce morbidity and mortality rates (359,363,381,382). Hypertension is also thought to contribute to renal disease in the general population (383–385). There is little reason to think that hypertension would not have similar adverse consequences for renal transplant recipients (386). An investigation of 29,751 cadaveric renal transplant recipients found that BP was a strong predictor of subsequent graft survival, whether or not death with a functioning graft was censored (372). Single-center studies have also linked adverse outcomes and posttransplant CVD to hypertension (327,366,387–390). However, there have been no large, randomized, controlled trials demonstrating that BP reduction improves outcomes after renal transplantation. Nevertheless, interventional trials have established the benefits of BP reduction in the general population, and BP is correlated with adverse outcomes after transplantation. Therefore, it is unlikely that trials comparing treated and untreated hypertension will be conducted among transplant recipients, because of ethical concerns.

Rationale. Standard measurement of BP in the clinic setting, as described by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (363), is probably most cost-effective. As a minimum,

Table 14. Aspirin prophylaxis for CVD

Rationale	The high incidence of CVD events warrants aggressive screening and intervention.
Recommendations	Patients with known ischemic heart disease should take aspirin or enteric-coated aspirin (65 to 325 mg/d) (A). Patients without known ischemic heart disease who are at high risk should take aspirin or enteric-coated aspirin (65 to 325 mg/d) (B).

Table 15. Hypertension

Incidence	50 to 80%
Consequences	Hypertension is associated with an increased incidence of CVD and decreased graft survival rates.
Rationale	The high prevalence of hypertension, its life-threatening consequences, and the effectiveness of antihypertensive therapy warrant aggressive BP screening.
Recommendations	BP should be measured at each office visit (A). BP should be maintained at <140 mmHg systolic and <90 mmHg diastolic (lower if possible) (A). BP in children should be less than the 95th percentile value for that age (B). BP self-measurement should be encouraged (B). Ambulatory BP monitoring may be useful for some patients (B).

BP should be checked during each office visit, using a mercury sphygmomanometer or recently calibrated aneroid manometer. Care should be taken to use BP cuffs of the appropriate size for children, because inaccurate results are obtained with cuffs that are either too large or too small. Automated methods of BP measurement may be necessary to obtain accurate results for infants. Self-measurement of BP provides valuable information. It helps to (1) distinguish sustained hypertension from “white-coat hypertension” (elevated BP in the clinic but not at other times), (2) assess responses to treatment, (3) improve adherence to treatment, and (4) reduce costs (363).

Ambulatory BP monitoring may also help distinguish white-coat hypertension. In addition, ambulatory BP monitoring may help detect nocturnal hypertension. Studies demonstrated that nocturnal hypertension is more common among dialysis patients than in the general population and that transplantation reduces the prevalence of nocturnal hypertension (391,392). However, other studies found that the prevalence of nocturnal hypertension is increased among transplant recipients, compared with the general population (393), and that CsA may contribute to posttransplant nocturnal hypertension (394). Few studies of the general population (363) and no studies of transplant recipients have investigated whether ambulatory BP monitoring predicts outcomes better than casual BP measurements. However, mean 24-h ambulatory BP values were found to be correlated more closely with left ventricular mass than were casual BP measurements in small studies of both pediatric and adult renal transplant recipients (395,396).

The prevalence of hypertension after renal transplantation is very high. Data from many observational studies and interventional trials have firmly established that hypertension contributes to CVD in the general population. Although there have been no large interventional trials proving that BP reductions are beneficial for renal transplant recipients, there are no compelling reasons to think that the relationship between hypertension and CVD would be different among renal transplant recipients, compared with the general population. Indeed, observational studies have linked hypertension to poor outcomes after renal transplantation. Guidelines for the treatment of hypertension in the general population are available (258,363,381,382,397–399). The National Kidney Foundation Task Force on CVD recommended that the goal for therapy should probably be $\leq 135/85$ mmHg for renal transplant recip-

ients without proteinuria and should possibly be $\leq 125/75$ mmHg for patients with proteinuria (386).

The specific treatment of posttransplant hypertension is not addressed in these guidelines. Most standard therapies have been demonstrated to be safe and effective after renal transplantation; however, there are a number of management issues that are unique to transplant recipients and are probably best addressed by experienced transplant physicians. For example, transplant recipients may be more prone to decreased renal function resulting from diuretic use than are hypertensive patients in the general population. Some calcium channel blockers alter the levels of calcineurin inhibitors. Patients may occasionally develop decreased renal function after angiotensin-converting enzyme inhibitor therapy, especially if the patients exhibit renal artery stenosis or chronic allograft nephropathy. Anemia and hyperkalemia may also be associated with the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists. Angiotensin-converting enzyme inhibitors have been reported to cause graft thrombosis and acute tubular necrosis (400,401), but these complications are probably rare.

A complete discussion of the screening and treatment of possible secondary causes of hypertension is also beyond the scope of these guidelines; however, when to screen for renal artery stenosis deserves some comment. Although renal artery stenosis may contribute to hypertension in many patients, treatment is invasive (375–377,402,403). Unless hypertension is difficult to control and/or renal function is compromised, it is probably not necessary to screen for allograft renal artery stenosis. Screening tests include color duplex sonography (376,404–409), captopril renography (376,404,410), magnetic resonance angiography (409,411), and spiral CT (412). Color duplex sonography appears to be the most cost-effective of these tests. The standard method for diagnosis is angiography.

Hyperlipidemia (Table 16)

Definition. According to the National Cholesterol Education Program (NCEP) guidelines, low-risk total and LDL cholesterol levels are <200 mg/dl and <130 mg/dl, respectively (413). High-risk total and LDL cholesterol levels are >240 mg/dl and >160 mg/dl, respectively. Low HDL levels are considered to be <35 mg/dl, whereas high fasting triglyceride levels are >200 mg/dl (413).

Table 16. Hyperlipidemia

Incidence	Approximately 60% of patients exhibit total cholesterol levels of >240 mg/dl (high risk).
Consequences	The role of hyperlipidemia in CVD is well established for the general population. Hyperlipidemia is associated with CVD in renal transplant recipients, and CVD is one of the most common causes of death after transplantation. Hyperlipidemia may also be associated with chronic allograft vasculopathy.
Rationale	The prevalence of hyperlipidemia is high enough to give screening tests sufficient positive and negative predictive values. The consequences of hyperlipidemia are of sufficient magnitude to make screening worthwhile. Effective treatment of hyperlipidemia is available.
Recommendations	Patients should be screened at least once during the first 6 mo and again at 1 yr after transplantation, with fasting total cholesterol, LDL, HDL, and triglyceride measurements. Thereafter, annual screening with total cholesterol measurements should be performed for patients with previously normal lipid levels and a low risk profile for CVD. Complete fasting lipid profiles should be obtained annually for individuals with borderline or previously high lipid levels. Changes in immunosuppressive therapy, graft function, or CVD risk may warrant additional screening (A).

Incidence. The prevalence of hyperlipidemia varies with the type of immunosuppressive medications used and other factors. In a report by the National Kidney Foundation Task Force on CVD, the prevalence of hyperlipidemia was estimated by combining the results of studies reporting the proportions of patients with lipoprotein levels above defined levels (414). In the combined results from five studies, 63% of 549 patients exhibited total cholesterol levels of >240 mg/dl (415–419). LDL cholesterol levels were >130 mg/dl for 60% of 769 patients (415,420,421). In contrast, HDL cholesterol levels were <35 mg/dl for only 12% of 777 patients (415,416,421,422). Triglyceride levels were >200 mg/dl for 36% of 1309 patients (415,416,418,422–424). Lipoprotein(a) measurements may help to identify patients who are at increased risk for CVD, although no therapy has been proven to be effective in reducing lipoprotein(a) levels. Lipoprotein(a) levels were >30 mg/dl for 23% of 468 patients (419,420,425–427). Information regarding lipid levels among pediatric renal transplant recipients is sparse. The North American Pediatric Renal Transplant Cooperative Study reviewed results for patients who were treated using a common immunosuppression protocol. Those investigators reported that, at 1 yr after transplantation, children did not exhibit elevated levels of total and VLDL cholesterol, compared with normal control subjects, and cholesterol levels (mean 213 mg/dl) were not high enough to require lipid-lowering agents (428). In contrast, a recent, long-term, retrospective study of 62 pediatric renal transplant recipients indicated that 52% of the patients exhibited elevated serum total cholesterol levels and 46% exhibited high LDL cholesterol levels (429). Additional studies are clearly warranted.

Consequences. It is generally accepted that total and LDL cholesterol cause ischemic heart disease in the general population. This conclusion is based on both observational studies and interventional trials (430). Increasing amounts of evidence implicate cholesterol in the pathogenesis of other CVD types as well. There have been no large-scale interventional trials among renal transplant recipients, but observational studies

identified correlations between hyperlipidemia and the high incidence of CVD after transplantation (325–327,431,432). Correlations between hyperlipidemia and chronic renal allograft dysfunction have also been reported. For example, Dimény *et al.* (433) observed that, for 151 patients, pretransplant cholesterol and triglyceride levels were correlated with chronic allograft nephropathy in biopsies obtained 6 mo after renal transplantation. In addition, cholesterol and triglyceride levels measured 4 yr after transplantation were associated with biopsy findings typical of chronic allograft nephropathy (434). Isoniemi *et al.* (435) reported that cholesterol and triglyceride levels measured 2 yr after transplantation predicted chronic allograft nephropathy at 4 yr after transplantation. Massy *et al.* (10) found the triglyceride level to be an independent risk factor for graft loss resulting from chronic allograft nephropathy. In a recent retrospective study, the serum cholesterol level was an independent predictor of death and death-censored allograft failure (436). Therefore, the clinical evidence is very strong, although not conclusive, that hyperlipidemia contributes to the incidence of CVD, death, and possibly death-censored allograft failure after renal transplantation (414).

Rationale. The National Kidney Foundation Task Force on CVD concluded that the high incidence of CVD, the strong association between hyperlipidemia and CVD, and the availability of effective lipid-lowering therapies make screening for hyperlipidemia after renal transplantation worthwhile (414). The NCEP recommends screening using nonfasting total and HDL cholesterol levels (413) and obtaining follow-up fasting lipid profiles for individuals with abnormal nonfasting levels. Although this strategy is reasonable, most transplant recipients have blood samples drawn after fasting for other reasons, *e.g.*, blood glucose screening for diabetes mellitus (see below). Therefore, the rationale for screening using nonfasting lipid measurements is less applicable to renal transplant recipients. The most useful screening tests for hyperlipidemia are fasting total cholesterol, LDL, HDL, and triglyceride measurements.

Lipid levels may change rapidly during the first 1 yr after transplantation. Therefore, screening at least twice during the

first 1 yr after transplantation seems prudent. Patients with pretransplant hyperlipidemia or patients at risk for hyperlipidemia because of the use of sirolimus may need to undergo screening more often. Screening relatively soon after transplantation may allow patients to receive adequate instruction and to begin lipid-lowering therapy before they return to caregivers who may not be comfortable with initiating lipid-lowering therapy for renal transplant recipients. The immunosuppressive medications, graft function, and proteinuria that influence plasma lipid levels often change during the posttransplant period. Therefore, periodic screening for hyperlipidemia beyond the first posttransplant year is warranted, particularly for individuals who are at high risk for CVD. Treatment should be based on the NCEP guidelines (413). Long-term studies of hyperlipidemia and its treatment in children are needed to provide evidence for recommendations.

Hyperhomocysteinemia (Table 17)

Definition. Fasting plasma total homocysteine (tHcy) levels of $>10 \mu\text{M}$ are generally considered to be abnormal (437,438). In the third National Health and Nutrition Examination Survey (1991 to 1994), high levels (exceeding gender-specific 95th percentiles) were $11.4 \mu\text{M}$ for men and $10.4 \mu\text{M}$ for women (439). What constitutes an abnormal increase in tHcy levels after methionine loading is unclear, but some have considered increases to levels that are >2 SD above the mean to be abnormal (437).

Incidence. Fasting tHcy levels are elevated in patients undergoing hemodialysis and decrease after transplantation (440,441). However, levels remain elevated, compared with the general population (441–446). Levels are inversely correlated with plasma folate and vitamin B6 and B12 levels (443,447–449) and even more so with renal function (high levels with decreased renal function) (441–443,448,449). Levels also tend to be higher for CsA-treated patients (442,447), but this association may not be as strong when the reduced renal function attributable to CsA is accounted for (447,448).

Consequences. The association between tHcy levels and CVD has been demonstrated by retrospective and prospective epidemiologic studies in the general population (437,450,451), and the evidence was recently critically reviewed (452). Ischemic heart disease, cerebral vascular disease, and peripheral

vascular disease are all more common among nontransplant patients with elevated fasting tHcy levels. Less clear is whether there is an additional association between post-methionine load increases in tHcy levels and CVD among nontransplant patients. A case-controlled study demonstrated that renal transplant recipients with CVD exhibited higher tHcy levels, compared with renal transplant recipients without CVD (453). Cross-sectional studies of renal transplant recipients reported a similar association between tHcy levels and CVD (447,448,454). Recently, a prospective observational study also found the tHcy level to be an independent risk factor for CVD (446). Although the association between tHcy levels and CVD in the general population is very strong and preliminary data suggest that a similar association might exist for renal transplant recipients, there are no interventional trials proving that lowering tHcy levels decreases the incidence of CVD.

Rationale. tHcy can be safely and effectively reduced by folate, vitamin B6, and vitamin B12 (455,456). Because CVD is associated with increased tHcy levels, therapy could be beneficial. However, the lack of well-designed interventional trials for any patient population makes it difficult to recommend routine screening.

Posttransplant Diabetes Mellitus (Table 18)

Incidence. The incidence of posttransplant diabetes mellitus is high but varies according to how diabetes mellitus is defined, the type of immunosuppressive medications used, age, and other factors. Posttransplant diabetes mellitus is caused primarily by glucocorticoids, CsA, and tacrolimus. In large prospective and retrospective studies, the incidences of posttransplant diabetes mellitus were 32 of 901 patients (3.6%) (280), 39 of 337 patients (11.6%) (457), 26 of 222 patients (11.7%) (458), and 30 of 167 patients (18.0%) (459). The incidence was reported to be higher among patients treated with CsA and prednisone, compared with azathioprine and prednisone (275,460); however, other investigators failed to confirm that finding (280). Tacrolimus has also been linked to posttransplant diabetes mellitus (461,462). Most cases of new onset diabetes mellitus occur within the first few months after transplantation (280,283,460). Older individuals (270,459,460,463) and black or Hispanic patients are most susceptible (270,283,312,457,461). One case-controlled study

Table 17. Hyperhomocysteinemia

Incidence	Although the upper limits of the normal range have not been clearly defined, renal transplant patients typically have fasting total homocysteine levels that are twofold higher than those of age- and gender-matched control subjects.
Consequences	An increasing amount of observational data for the general population suggest that elevated total homocysteine levels are associated with CVD. There are, however, no controlled clinical trials demonstrating that lowering homocysteine levels reduces CVD risk.
Rationale	The incidence is high enough to warrant screening. Although it is not known whether normalization of homocysteine levels reduces CVD risk, detection of elevated homocysteine levels may help identify patients at risk for CVD and thereby suggest patients who would benefit from the management of risk factors for which treatment is known to reduce CVD risk.
Recommendations	There is insufficient evidence for or against measuring homocysteine levels (C).

Table 18. Posttransplant diabetes mellitus

Incidence	3.6 to 18%
Consequences	Diabetes mellitus is associated with CVD, infections, retinopathy, nephropathy, and neuropathy.
Rationale	Given the increased incidence of posttransplant diabetes mellitus and the availability of a simple screening test, fasting blood glucose levels should be checked regularly. The benefits of strict glycemic control on long-term morbidity and mortality rates and, by inference, the benefits of early detection and treatment of diabetes mellitus justify frequent screening.
Recommendations	Fasting blood glucose levels should be measured at least weekly for months 1 to 3, at least every other week for months 4 to 6, and at least monthly for months 6 to 12. After the first posttransplant year, fasting blood glucose and/or glycosylated hemoglobin levels should be measured at least yearly (A).

suggested that patients with adult polycystic kidney disease were more likely to develop posttransplant diabetes mellitus (464).

Consequences. Diabetes mellitus is a major cause of morbidity and death. There is no reason to think that posttransplant diabetes mellitus produces fewer complications than diabetes mellitus in other settings, and at least one study has indicated that the consequences of posttransplant diabetes mellitus are similar to those of pretransplant diabetes mellitus (465). Some studies have reported that patients with posttransplant diabetes mellitus experience decreased allograft survival (282,460).

Rationale. The most readily available and cost-effective screening test is fasting blood glucose level measurement. Glycosylated hemoglobin level measurement is also proving to be an effective test for screening (466). The oral glucose tolerance test is still the standard test for diagnosing diabetes mellitus but is less than optimal for routine screening because of its cost and inconvenience. The American Diabetes Association recommends screening by measuring fasting plasma glucose levels (467). A plasma glucose level of >126 mg/dl is an indication for diagnostic testing (467). Strict glycemic control decreases retinopathy, nephropathy, neuropathy, and possibly CVD in nontransplant patients with diabetes mellitus (468). By inference, the early detection, prevention, and treatment of diabetes mellitus may reduce the frequency of these complications in renal transplant recipients. It is likely that the screening and early detection of posttransplant diabetes mellitus will help control and prevent the complications of diabetes mellitus and thereby decrease morbidity and mortality rates. The National Kidney Foundation Task Force on CVD concluded that strict control of posttransplant diabetes mellitus in the absence of advanced age or comorbid conditions was warranted (469).

Cigarette Smoking (Table 19)

Incidence. The prevalence of cigarette smoking after renal transplantation is comparable to that found in the general population (470).

Consequences. Retrospective observational studies have linked smoking to CVD (325,470), decreased patient survival (470–472), and graft failure (473).

Rationale. Evidence from studies in the general population strongly suggests that cigarette smoking increases the risk for CVD and malignancies. The morbidity and mortality rates for both of these complications are higher after renal transplantation, compared with the general population. Moreover, some observational studies have linked smoking to adverse outcomes after renal transplantation. Because intervention is often effective, cigarette smoking should be screened for and treated in renal transplant recipients. Guidelines have been developed for smoking cessation (474–476).

V. Bone and Bone Marrow

Erythrocytosis (Table 20)

Definition. Erythrocytosis is usually defined as a hemoglobin level of >17 to 18 g/dl or a hematocrit value of >51 to 52%.

Incidence. The reported incidence is variable, but most studies report that it is between 10 and 20%. Specifically, studies have reported that the incidence of erythrocytosis after renal transplantation is 8.1% (477), 9.8% (478), 11% (479), 12.4% (480), 13.5% (481), 17.3% (482), and 21.6% (483). The incidence seems to be somewhat higher in the first 1 yr after transplantation (477).

Consequences. Some retrospective epidemiologic studies suggested that higher hematocrit values are associated with an increased risk of thromboembolic events after renal transplan-

Table 19. Cigarette smoking

Incidence	Similar to that observed for the general population.
Consequences	Cigarette smoking has been linked to CVD, malignancies, and possibly graft dysfunction.
Rationale	Given the increased risk for CVD and malignancy, efforts directed at preventing and treating cigarette abuse are likely to be even more beneficial than in the general population.
Recommendations	At least annual screening should be performed, following the guidelines of the Agency for Health Care Policy and Research (A).

Table 20. Erythrocytosis

Incidence	10 to 20%
Consequences	Erythrocytosis may increase morbidity and mortality rates.
Rationale	Erythrocytosis causes potentially life-threatening complications and is readily treatable. The incidence is high enough to warrant routine screening.
Recommendations	Hemoglobin levels and hematocrit values should be measured at least weekly for months 1 to 2, at least every other week for months 3 to 4, at least monthly for months 4 to 12, and then at least once every 3 to 6 mo (B).

tation (325,479,482), but at least one study failed to confirm that finding (484). Among nontransplant patients, epidemiologic studies clearly demonstrated an increased incidence of CVD complications for patients with polycythemia rubra vera (485–488). Although there have been few large, randomized, controlled trials, interventions that reduce hematocrit values seem to reduce the incidence of CVD events among patients with polycythemia rubra vera (485,487).

Rationale. The incidence of erythrocytosis among renal transplant recipients seems to be high, and the consequences may be life threatening. In addition, effective therapies are available for patients with marked erythrocytosis. In particular, angiotensin-converting enzyme inhibitors (489–496) or angiotensin II receptor antagonists (497,498) have been demonstrated to consistently reduce elevated hematocrit values. Theophylline may also be effective (499–501). If these therapies are not sufficient, phlebotomy can effectively correct erythrocytosis and help prevent its complications (502). Surgical removal of the native kidneys may also be a treatment option in some cases (503).

Anemia (Table 21)

Definition. Anemia is usually defined as hemoglobin levels of <13 g/dl (hematocrit of 42%) for male patients and <12 g/dl (hematocrit of 37%) for female patients (504). Normal hemoglobin levels in children are age-related and generally are lower than normal levels for adults.

Incidence. The incidence of anemia after renal transplantation is not well documented. However, most authors report that anemia is relatively common early after transplantation. It is also common late after transplantation among patients with chronic graft dysfunction. The incidence was 12% (hematocrit of <33%) in one study (505).

Consequences. Common, potentially reversible causes of anemia include bone marrow suppression resulting from immunosuppressive agents (especially but not exclusively MMF and azathioprine) (506,507), iron deficiency (505,508–511), and the use of angiotensin-converting enzyme inhibitors (512–515) or angiotensin II receptor antagonists (497,516). Allograft dysfunction is a frequent contributing factor to anemia early and late after renal transplantation (505,509,517). Erythropoietin deficiencies and erythropoietin resistance that are not associated with decreased renal function may occur in some patients (518). The differential diagnosis of anemia also includes many potentially life-threatening disorders that are amenable to treatment and need to be detected as quickly as possible. These include (but are not limited to) gastrointestinal bleeding, malignancies, autoimmune hemolytic anemia (519–521), and some rare disorders, such as B19 parvovirus infection (522–524). CMV infection is frequently associated with anemia but is usually symptomatic and therefore is not a reason to screen for anemia itself. Folate and vitamin B12 deficiencies may cause or contribute to anemia.

Rationale. Because removal of its underlying cause can often reverse anemia, screening for anemia is particularly important. When there is no reversible underlying cause, subcutaneous treatment with human recombinant erythropoietin is both safe and effective (525–529). Studies in nontransplant patient populations, *e.g.*, patients undergoing hemodialysis, have unequivocally demonstrated that correction of anemia improves the quality of life. At least one study has confirmed that correction of anemia improves the quality of life for renal transplant recipients (528). Although the true incidence of anemia is poorly defined, it appears to be high enough to make screening an effective tool after renal transplantation.

Table 21. Anemia

Incidence	High (probably >10%)
Consequences	Anemia is associated with increased morbidity and mortality rates.
Rationale	Anemia causes increased morbidity after renal transplantation, and effective interventions are available. In addition, the detection of anemia may lead to the discovery of other underlying treatable diseases that can cause morbidity and death. The incidence, although poorly documented, is probably high enough to make routine screening effective.
Recommendations	Patients should be screened at least weekly for months 1 to 2, at least every other week for months 3 to 4, at least monthly for months 4 to 12, and then at least once every 3 to 6 mo (B).

Table 22. Osteoporosis

Incidence	Up to 60%
Consequences	Osteoporosis may cause bone pain and fractures.
Rationale	There is effective treatment for corticosteroid-induced bone mineral density loss, which may reduce the incidence of fractures and bone pain.
Recommendations	Lumbar spine and hip bone mineral densities should be measured by dual x-ray absorptiometry at the time of transplantation, after 6 mo, and then every 12 mo if results are abnormal (B).

Osteoporosis (Table 22)

Definition. Osteoporosis is defined as bone mineral density >2.5 SD below the young adult mean value (t-score).

Incidence. As many as 60% of kidney transplant recipients treated with corticosteroids may lose sufficient bone mineral density to meet the definition of osteoporosis in the first 18 mo after transplantation (530–543). Bone demineralization may then improve or persist at a slower rate (286,540,544–550). In a recent cross-sectional study, 55 patients underwent bone densitometric examinations and bone biopsies a mean of 10 yr after transplantation (551). None exhibited decreased axial bone mineral density, but most exhibited decreased femoral neck bone mineral density (551). In biopsies, 46.5% of patients exhibited mixed uremic osteodystrophy, 23.2% exhibited adynamic bone disease, 13.9% exhibited hyperparathyroid disease, and only 16.3% exhibited normal bone (551). Bone fractures are late complications in the current era, occurring in approximately 10% of recipients an average of 8 yr after kidney transplantation (286,552–554). In contrast, bone fractures are common early complications among patients with insulin-dependent diabetes mellitus who undergo combined kidney-pancreas transplantation, occurring in approximately 50% of recipients within the first 5 yr after transplantation (555).

Consequences. Bone pain and fractures occur both in vertebral bone and in peripheral bone (286). In a recent retrospective cross-sectional study of 193 renal transplant recipients, 17% developed fractures attributable to osteoporosis after 0.5 to 23 yr of follow-up monitoring (556). Fractures were more common among patients with type 1 diabetes mellitus (40%), compared with nondiabetic patients (11%) (556). The foot has been the most common fracture site in combined kidney-pancreas transplant recipients (555). The bone mineral density

fracture risk threshold for kidney transplant recipients has not been defined (534). Threshold values in the general population are 0.900 g/cm² for the lumbar sacral spine and 0.600 g/cm² for the femoral neck.

Rationale. Lumbar spine and hip bone mineral density measurements by dual x-ray absorptiometry are readily available in most areas. There are few data on the value of serum biochemical markers of bone metabolism after renal transplantation (557,558). Bone loss after kidney transplantation is predominately a consequence of corticosteroid-induced decreases in bone formation. CsA caused high-turnover bone disease in an experimental animal model (559), but firm clinical evidence of this disorder is lacking (560). Secondary hyperparathyroidism and aluminum bone disease (which is becoming increasingly uncommon) may be contributing factors (533).

Corticosteroid-induced osteoporosis is time- and dose-dependent. Bone demineralization is rapid in the early months after transplantation, when corticosteroid doses are highest (535–543). Bone loss may stabilize or persist >2 yr after transplantation (286,540,544–549). Effective treatment of corticosteroid-induced bone loss is now available, but there are few randomized controlled trials examining preventive strategies for osteoporosis among renal transplant recipients (561,562).

Secondary Hyperparathyroidism (Table 23)

Incidence. Up to 10 to 20% of recipients may develop hypercalcemia within the first 1 to 2 yr after transplantation (563–566). The incidence of refractory posttransplant hyperparathyroidism may be decreasing with better pretransplant management of secondary hyperparathyroidism (567).

Table 23. Secondary hyperparathyroidism

Incidence	Ten to 20% of patients may develop hypercalcemia.
Consequences	Hyperparathyroidism may cause symptomatic hypercalcemia, renal dysfunction, soft-tissue calcification, and bone demineralization.
Rationale	The incidence of hyperparathyroidism is high enough and the consequences are severe enough to warrant routine screening. Effective medical and surgical therapies are available.
Recommendations	Serum total calcium levels should be measured at least monthly during the first 6 mo, every 2 mo until the end of the first 1 yr, and then annually until normal. For patients with low serum albumin levels, total calcium levels should be corrected or ionized calcium levels should be measured directly (A). Serum intact parathyroid hormone levels should be measured at 6 and 12 mo and then annually (A).

Consequences. Symptomatic hypercalcemia, renal allograft dysfunction, hypertension, soft-tissue calcification, and bone demineralization attributable to high-turnover bone disease (568,569) may all result from secondary hyperparathyroidism. It is theoretically possible that secondary hyperparathyroidism may contribute to the high incidence of CVD among patients with renal disease.

Rationale. Secondary hyperparathyroidism persists after transplantation, because involution of parathyroid gland hyperplasia is slow and may never occur, despite the re-establishment of renal function (569). Glandular involution and the return to basal parathyroid hormone secretion may take years. Hypercalcemia is usually evident within the first 1 yr after transplantation (563,566). Up to 5% of transplant recipients may require a parathyroidectomy for control of progressive bone demineralization, symptomatic hypercalcemia, or asymptomatic moderate hypercalcemia (total serum calcium levels of ≥ 12 to 12.5 mg/dl) (565,566,570,571). Calcium and vitamin D therapy may accelerate the return to basal parathyroid hormone secretion (572,573).

VI. Nutrition and Metabolism

Hypophosphatemia (Table 24)

Definition. Hypophosphatemia is defined by serum phosphorus levels of <2.6 mg/dl (504).

Incidence. Hypophosphatemia is very common in the early weeks after transplantation (574). The decrease in serum phosphorus levels is less among transplant recipients who receive corticosteroid-free immunosuppressive therapy (574). Its prevalence decreases with time after transplantation, but mild hypophosphatemia may persist indefinitely for $>50\%$ of recipients (575–578).

Consequences. Muscle weakness and possibly osteomalacia may occur (578–580). Most recipients are asymptomatic.

Rationale. Hypophosphatemia is primarily a result of phosphaturia resulting from persistent hyperparathyroidism, corticosteroid effects on renal phosphate reabsorption (576), and a parathyroid hormone-independent renal “leak” of phosphorus (575,577). Intestinal malabsorption of dietary phosphorus may also occur (581,582). The use of phosphorous-binding antacids may also interfere with the intestinal absorption of phosphorous. A small ($n = 28$), randomized, controlled trial demonstrated that replacement therapy with orally administered neutral phosphate for 12 wk restored muscular phosphorous content, increased tissue ATP levels, and improved metabolic acidosis (through increased urinary titratable acidity), without adverse effects (583).

Hypomagnesemia (Table 25)

Definition. Hypomagnesemia is defined by serum total magnesium levels of <1.5 mg/dl (504).

Incidence. Up to 25% of long-term CSA-treated recipients manifest hypomagnesemia, which is usually mild (584). The prevalence decreases with time after transplantation, possibly because of decreasing CsA blood levels (585–587). Markell *et al.* (587) found that ionized magnesium levels were low, even when total magnesium levels were near normal, and ionized magnesium levels were especially low in patients with high levels of CsA. Other investigators have confirmed these findings (588). The prevalence of CsA-induced hypomagnesemia may be higher among diabetic patients (588).

Consequences. Muscle weakness, hypokalemia, hypocalcemia, and (rarely) seizures may result from hypomagnesemia. Low serum magnesium levels may be associated with hypertension in CsA-treated patients (586). Low magnesium levels have also been linked to hyperlipidemia. Indeed, magnesium replacement improved the lipid profiles of nontransplant patients with ischemic heart disease in a double-blind, randomized, controlled trial (589). Low magnesium levels have also been linked to hyperlipidemia in renal transplant recipients and, in a small uncontrolled trial, magnesium replacement was demonstrated to reduce elevated total and LDL cholesterol levels (590). It has been suggested that low magnesium levels could contribute to the toxicity of CsA (587).

Rationale. Hypomagnesemia can result from CsA- or tacrolimus-induced renal magnesium leaks (584,591). The use of thiazide diuretics is another common cause of renal magnesium loss. Hypomagnesemia may have several adverse consequences. Oral magnesium supplements are readily available.

Hyperuricemia (Table 26)

Definition. Hyperuricemia is defined by serum uric acid levels of >6.6 mg/dl in women and >8.5 mg/dl in men (504).

Incidence. In a randomized controlled trial, 80% of 131 patients allocated to receive CsA and prednisone developed serum uric acid levels of >8.0 mg/dl, compared with 55% of 115 patients allocated to receive azathioprine, prednisone, and antilymphocyte globulin (592). In a retrospective study, 84% of 129 CsA-treated patients developed hyperuricemia (uric acid levels of >6.7 mg/dl in women and >7.9 mg/dl in men), compared with 30% of 168 azathioprine-treated transplant recipients (593). In another retrospective study, after exclusion of patients with gout, 67% of 211 CsA-treated patients developed hyperuricemia (uric acid levels of >7.0 mg/dl in women and >8.0 mg/dl in men), compared with 32% of 32 patients

Table 24. Hypophosphatemia

Incidence	More than 50% of long-term recipients may exhibit mild hypophosphatemia.
Consequences	Hypophosphatemia may cause muscle weakness and possibly osteomalacia.
Rationale	Hypophosphatemia is very common, and the consequences are severe enough to warrant routine screening. Effective treatment is available.
Recommendations	Serum phosphorous levels should be measured at least monthly during the first 6 mo, every 2 mo until the end of the first 1 yr, and then annually (A).

Table 25. Hypomagnesemia

Incidence	Approximately 25% of long-term CsA-treated recipients develop hypomagnesemia, which is even more common among patients treated with loop diuretics.
Consequences	Hypomagnesemia may cause muscle weakness, hypokalemia, hypocalcemia, cardiac dysrhythmias, and possibly hypertension and neurotoxicity.
Rationale	Hypomagnesemia is common, the consequences are potentially severe, and treatment is available.
Recommendations	Patients should be screened monthly for the first 6 mo and then every 6 to 12 mo. Patients treated with large doses of diuretics should be screened more often (A).

Table 26. Hyperuricemia

Incidence	Up to 80% of patients treated with CsA may develop hyperuricemia. Hyperuricemia is especially common among patients with reduced renal function and patients treated with diuretics.
Consequences	Hyperuricemia may cause gout (common), nephrolithiasis (unusual), and renal failure (rare).
Rationale	Screening to detect patients with very high levels of uric acid may allow preemptive measures to be taken to prevent complications.
Recommendations	Serum uric acid levels should be measured at least once during the first 2 to 3 mo after renal transplantation. Additional screening may be warranted for patients with reduced renal function and patients treated with diuretics (B).

treated with azathioprine (594). In that study, the incidence of hyperuricemia was higher among patients treated with diuretic agents (594). Hyperuricemia is also common among pediatric renal transplant recipients, being found in 39% of 81 patients at 6 mo after transplantation (595). Most authors have reported that elevated uric acid levels result from decreased renal excretion (596–599), and serum uric acid levels are inversely correlated with renal function (595,597,598,600).

Consequences. Gout was observed for 6 of 131 patients (4.6%) randomly allocated to receive CsA, compared with 0 of 115 patients randomly allocated to receive azathioprine (592). In a retrospective study, 9 of 129 CsA-treated patients (7%) developed gout, compared with 0 of 168 patients treated with azathioprine (593). In another retrospective study, 25 of 211 CsA-treated patients (11.8%) developed gout, compared with 0 of 32 patients treated with azathioprine (594). In a similar retrospective study, gout developed in 13 of 55 CsA-treated patients (24%), compared with 0 of 23 azathioprine-treated patients. In another retrospective study, 13 of 133 CsA-treated patients (9.9%) developed gout, compared with 0 of 81 patients treated with azathioprine (597). In a randomized trial of CsA withdrawal, gout developed in 9 of 68 patients (13.2%) who continued to receive CsA, compared with 1 of 60 azathioprine-treated patients (1.6%) (601). Hyperuricemia has been linked to adverse outcomes in one (602) but not in another (592) retrospective study. In a case report, renal allograft failure was attributed to hyperuricemia (603). Other authors reported urolithiasis associated with hyperuricemia after renal transplantation (604).

Rationale. Except for gout, the incidence of adverse consequences associated with hyperuricemia appears to be very low. Therefore, it can be argued that serum uric acid levels need only be measured for patients suspected of having gout or other potential complications of hyperuricemia. Indeed, mild to

moderate hyperuricemia in asymptomatic patients may not warrant treatment, because gout is uncommon among those patients. Markedly elevated levels of serum uric acid could lead to nephrolithiasis as well as gout. Intervention may be appropriate for asymptomatic patients with markedly elevated serum uric acid levels. Therefore, it is reasonable to screen transplant recipients to detect the occasional patients with very high uric acid levels. These high levels are most likely to occur early after transplantation in patients treated with CsA and diuretics.

Malnutrition and Obesity (Table 27)

Incidence. Approximately 10% of patients exhibit hypoalbuminemia at 1 yr after transplantation (605). The prevalence of low serum albumin levels increases in the late post-transplant period, to >20% by 10 yr after transplantation. In a study of 232 kidney-pancreas transplant recipients, hypoalbuminemia was present in 15% at 1 yr and 8% at 3 yr (606). Many studies report the prevalence of obesity at the time of transplantation but few report its prevalence after transplantation. In two small studies, both diabetic and nondiabetic renal transplant recipients gained an average of 6 to 8 kg by 2 yr and an average of 9 to 10 kg by 3 yr after transplantation (607,608). One retrospective study of 115 renal transplant recipients found that only 21% were obese at the time of transplantation but 43% were overweight 1 yr after transplantation (609).

Consequences. At least one cross-sectional study of renal transplant recipients found that low serum albumin levels were associated with poor long-term outcomes after renal transplantation (605). Similar results were reported for kidney-pancreas transplant recipients (606). Obesity at the time of transplantation was associated with worse outcomes in most (609–614)

Table 27. Malnutrition and obesity

Incidence	Malnutrition: 10% of patients exhibit low serum albumin levels at 1 yr and 20% at 10 yr after transplantation, although factors other than caloric intake may contribute to hypoalbuminemia. Obesity: approximately 40% of renal transplant recipients are obese 1 yr after transplantation.
Consequences	Malnutrition is associated with an increased risk of infection, delayed wound healing, muscle weakness, and general debility. Obesity may have adverse effects on CVD and is associated with poor wound healing.
Rationale	Both malnutrition and obesity may have adverse consequences that may be ameliorated with diet or other interventions.
Recommendations	Height, weight, and body mass index should be recorded and history assessments and physical examinations should be performed (A). Serum albumin levels should be measured at least 2 or 3 times in the first posttransplant year and then annually (B). Serum prealbumin levels should be measured if albumin levels are low or if clinical findings suggest possible malnutrition (B).

but not all (615,616) studies. However, few studies have examined the effects of posttransplant weight gains on outcomes.

Rationale. Serum albumin levels can be easily measured in most laboratories. Low serum albumin levels may be the result of decreased production and/or increased catabolism, both of which are frequently associated with malnutrition. Increased urinary protein excretion may also result in low serum albumin levels. Hepatic synthesis of prealbumin (transthyretin) is very sensitive to the adequacy of protein and energy intake, and serum prealbumin levels may be a good measure of nutrition (617,618). However, levels of prealbumin, like other plasma proteins, may be affected by inflammation and other factors (619). There are virtually no studies examining prealbumin levels in renal transplant recipients, but prealbumin levels appear to predict outcomes in other populations (620), including patients with ESRD (621). Weight loss, evidence of muscle wasting, and the clinical setting may also suggest malnutrition.

Corticosteroids accelerate the protein catabolic rate and frequently create a negative nitrogen balance (622). Studies have documented significant increases in the protein catabolic rate, accompanied by decreases in serum albumin levels, in the immediate posttransplant period (622,623). Even low-dose maintenance corticosteroid therapy increases protein catabolism and muscle wasting. In one study, renal transplant recipients with stable kidney function exhibited mid-arm muscle circumference values below the 5th percentile (608). Chronic allograft nephropathy is associated with decreases in muscle mass, which are reflected in decreases in urinary creatinine excretion (44).

Increased caloric intake may also occur after transplantation (624), primarily because of enhanced appetite associated with corticosteroid use. Obesity may contribute to cardiovascular risks and other complications. Obesity can be detected by physical appearance during examinations, as well as by measurements of height, weight, and body mass index (weight in kilograms divided by height in meters squared). Guidelines for identifying and managing obesity have been developed by the National Heart, Lung, and Blood Institute (625). These guide-

lines suggest that body mass index values be measured to assess obesity (category C evidence). Weight loss is recommended to improve lipid profiles, lower BP, and improve glycemic control for patients with type II diabetes mellitus (each category A evidence) (625). A low-fat, low-calorie diet is recommended (category A), with exercise (category A) (625). The United States Preventive Services Task Force recommended that periodic height and weight measurements, with body mass index values or published tables for normal ranges, be used to screen for obesity (category B evidence) (626).

Both malnutrition and obesity are common enough to suggest that screening could be effective. Although there have been no studies demonstrating that intervention can improve nutrition and outcomes after renal transplantation, studies in the general population provide sufficient evidence to suggest that interventions may be effective. Few studies have examined the success of diet alterations in correcting posttransplant weight gains (627).

Growth and Development of Children (Table 28)

Definition. Children of different ages grow at different rates. The fastest growth occurs in the first 2 yr of life and during puberty. Growth failure is defined as a height >2 SD below the normal value for that age, a height velocity SD score (SDS) of -2.0 , or an absolute growth rate of <4 cm/yr. The development of young children is assessed as the achievement of certain landmarks of fine motor, gross motor, social, and communication skills, compared with age-specific normal findings. School function, again compared with age-matched peers, is the best measure of development for older children.

Incidence. Children typically develop growth failure early in the course of ESRD. A survey of the European Dialysis and Transplantation Registry demonstrated that 50% of patients exhibited a final adult height below the 3rd percentile, with some advantage being observed for the children who received renal transplants (628,629). In a North American Pediatric Renal Transplant Cooperative Study analysis of 1768 children with GFR of <75 ml per min per m^2 , more than one-third exhibited a height deficit of >2 SDS. It has been amply

Table 28. Growth and development of children

Incidence	Most children experience growth failure and delayed development after renal transplantation.
Consequences	Children may not reach their expected final adult height or their expected educational or developmental potential.
Rationale	Although the incidence of growth failure and delayed development is high, there are several steps that can be taken to improve growth and development. Therefore, close monitoring of growth and development and intervention as necessary are warranted.
Recommendations	Height and weight should be recorded at each visit. Height and weight should be measured at least every 3 mo for children <3 yr of age and every 6 mo for children >3 yr of age until they reach their final adult height (B). Children <5 yr of age should undergo formal developmental testing at least every 4 mo, to allow early intervention if warranted (B). School-age children should be assessed for school function twice each year (B).

demonstrated that chronic renal insufficiency beginning in infancy leads to permanent reductions in growth potential (630). Growth retardation continues in children undergoing dialysis (peritoneal dialysis or hemodialysis). It has been suggested that a functioning transplant should enable the child to achieve catch-up growth (631,632). Unfortunately, long-term registry data on growth have been disappointing. The North American Pediatric Renal Transplant Cooperative Study tracked growth after transplantation longitudinally, using the same cohort, for at least 5 yr. The height deficit was -2.41 SD at 2 yr, -2.46 SD at 3 yr, and -2.29 SD at 54 mo. Children experienced improvements in height SDS of $+0.18$ at 2 yr, $+0.16$ at 3 yr, and $+0.11$ at 54 mo. When improvements in height deficits were evaluated according to donor source, no differences were noted between living-related and cadaver donor recipients. Analysis of height SDS according to race revealed that, whereas steady improvements were noted at 2 yr and 54 mo for Caucasian children, there was an actual deceleration of growth for African American and Hispanic children. Only the initial height deficit and recipient age were independent predictors of improved height after transplantation. Catch-up growth, defined as an improvement of 1 SDS, was observed only for children 0 to 1 yr of age. Overall, catch-up growth was observed for only 47% of children between the

ages of 2 and 5 yr. For children >5 yr of age (72% of the study cohort), little catch-up growth was noted (292).

During the first 2 yr of life, the brain more than doubles in volume and attains 80% of its final size. Children who develop renal failure early in life are at serious risk for neurologic dysfunction (633,634). In children, verbal performance and memory function are decreased (635,636). Test performance generally improves after transplantation (635,637). In general, the proportion of patients who achieve success in higher education is less than that in the general population or that of patients with other chronic diseases, such as diabetes mellitus (638). There is some indication that the long-term results of rehabilitation after kidney transplantation are improving (639–641). However, all ages report problems with usual daily activities (642).

Consequences. Although transplantation can temporarily restore normal renal function to children with ESRD, residual somatic and neurologic damage and the requirements for long-term medication administration prevent complete and long-lasting rehabilitation. Therefore, the majority of children do not attain normal height. Furthermore, cognitive functioning is affected and the problems associated with chronic disease management interfere with complete rehabilitation.

Table 29. Cancers of the skin and lip

Incidence	May exceed 40 to 60% by 20 yr after transplantation.
Consequences	Multiple, recurrent, and aggressive skin cancers can cause severe local tissue destruction and metastases to lymph nodes and distant sites. Approximately 5% of renal transplant recipients with skin cancer die as a consequence of their malignancies.
Rationale	Early diagnosis is the best method currently available to prevent morbidity and death associated with skin cancer. Many patients with skin malignancies that are diagnosed and treated in the early stages can survive and remain free of disease.
Recommendations	Self-examination of the skin should be performed monthly (B). Examination of the skin by a physician should be performed at least yearly, with early referral of suspected lesions (B). Patients should be counseled to prevent skin damage by avoiding sun exposure and using appropriate sunscreens (B).

Rationale. There are several possible approaches to treating growth failure after renal transplantation, such as discontinuation of prednisone administration (292), alternate-day steroid therapy (289,290,643), or the use of recombinant human growth hormone (644,645), but none are universally accepted. However, close monitoring of growth for all children is mandatory, so that treatment may be provided if necessary. Furthermore, formal psychologic and developmental testing is necessary to provide support for rehabilitation that is as complete as possible.

VII. Cancers

Cancers of the Skin and Lip (Table 29)

Definition. Malignant skin lesions common among renal transplant recipients include squamous cell carcinomas, basal cell carcinomas, malignant melanomas, and Merkel cell tumors (646). Kaposi's sarcomas (KS) frequently involve the skin but are discussed below.

Incidence. Carcinomas of the skin and lip are the most common malignancies among adult renal transplant recipients (647–650). As many as 40 to 53% of all malignancies among transplant recipients are skin and lip cancers (649,651). The incidence of skin cancer varies with the amount of sun exposure and the length of follow-up monitoring after transplantation (646). In regions with limited sun exposure, such as the Netherlands, the risk of a first skin tumor is 10% at 10 yr after transplantation and 40% at 20 yr (652). In regions with increased sun exposure, such as Australia, the incidence is 66% by 23 yr after transplantation (653).

In the general population, basal cell carcinoma is the most common malignant skin tumor (654). Basal cell carcinomas outnumber squamous cell carcinomas by ratios of 5:1 to 8:1 in the general population, but squamous cell carcinomas outnumber basal cell carcinomas by ratios of 1.1:1 to 1.8:1 among renal transplant recipients (647,652). The overall incidence among renal transplant recipients is 250 times higher for squamous cell carcinoma and 10 times higher for basal cell carcinoma, compared with the general population (652). Patients treated with dialysis do not exhibit a higher incidence of skin cancer, compared with the general population, and cohorts of patients for whom immunosuppression is withdrawn after allograft failure exhibit a much lower incidence of skin cancer, compared with cohorts of patients with functioning grafts (655).

Malignant melanomas also occur with increased frequency among renal transplant recipients (654,656). They represent 5% of posttransplant skin cancers, compared with 2.7% of skin cancers in the general population (657). Most malignant melanomas in transplant recipients originate in the skin (657). Malignant melanomas are the most important tumors that are inadvertently transmitted with transplanted organs (657). Malignant melanomas can recur after transplantation among patients who were treated for the disease several years before transplantation (657).

The risk of lip cancer is increased up to 29-fold, compared with the general population (650). In a study of 160 renal transplant recipients, 13% exhibited leukoplakia; of those with

leukoplakia who underwent biopsies, 62% exhibited dysplastic lesions and 10% squamous cell carcinoma of the lip (658). Sun exposure and smoking were identified as risk factors.

In one long-term study of pediatric organ transplant recipients, skin cancer was the second most common malignancy (659). Malignant melanoma and lip cancer are more common among pediatric transplant recipients than adult recipients.

Immunosuppressive therapy, ultraviolet radiation, and infection with human papillomavirus (HPV) are risk factors for skin cancer (646,652). Skin cancer among transplant recipients is more common in regions with abundant sun exposure, especially for fair-skinned individuals. The association between total sun exposure (before and after transplantation) and the risk of developing skin cancer (648,660) may be linked to mutations in the *p53* gene (661). There is a high prevalence of *p53* immunoreactivity in premalignant and malignant skin lesions in renal transplant recipients, suggesting a role for *p53* protein in skin cancers (662).

Immunosuppression contributes to the development of skin malignancies (647,663,664). Renal transplant recipients with cutaneous malignant melanomas are unable to mount appropriate cellular immune responses to neoplastic cells (654). The role of the immune system in skin cancer is further emphasized by the noted association between MHC-DR1 and basal cell carcinomas in the general population (665). For renal transplant recipients, an association between MHC-B mismatching and the development of skin cancer that was reported for Dutch patients (666,667) could not be confirmed in a study of Australian patients (668). MHC-B27, MHC-DR7, and MHC-DQw2 are associated with an increased risk of cancer among renal transplant recipients, whereas there has been a negative association between MHC-DA11 and skin cancer (667,669).

Infection by HPV has also been postulated to be an important factor in the development of skin cancer among renal transplant recipients (646). Warts have been noted in up to 75% of renal transplant recipients, and HPV has been isolated from 43% of warts (660). HPV has been detected in close to 60% of nonmelanoma skin cancers in renal transplant recipients (670). A broad spectrum of HPV types and multiple viral types in the same specimen have been noted in biopsies of skin lesions from transplant recipients (660,670–672). Nevertheless, it is not clear to what extent HPV contributes to the development of skin cancer among renal transplant recipients (673,674).

Consequences. Skin cancers are more aggressive in transplant recipients than in the general population (647). The incidence of multiple cancers is high, and many patients have several different types of skin malignancies that are prone to recurrence and metastasis (646,648). The onset of squamous cell and basal cell carcinomas occurs at a younger age among transplant recipients, compared with the general population (675,676).

Lymph node metastases have been reported to occur in 5.8 to 7% of transplant recipients with squamous cell carcinoma of the skin (647,663), and approximately 5% die as a result. Lymph node metastases occur in 20% of patients with malignant melanoma, and 30% ultimately die as a result of their

malignancies. Overall, approximately 5% of transplant recipients with skin carcinomas that were reported to the Cincinnati Transplant Tumor Registry died as a result of their skin malignancies, compared with 1 to 2% of cancer-related deaths in the general population (647). Basal cell carcinomas rarely metastasize but do cause local tissue destruction, which may lead to disfigurement or functional impairment (654).

Rationale. The incidence of skin cancer among renal transplant recipients is high, and morbidity and mortality rates are much higher than those for the general population. Skin cancers can be detected clinically and can often be cured by excision. Most renal transplant recipients with cutaneous malignant melanomas that are diagnosed early survive and remain free of disease (654,657). Early diagnosis is currently the best method to alter the course of malignant melanomas among renal transplant recipients (677). Early diagnosis is also the best method to alter the course of other skin malignancies.

Examination of the skin is the principal screening test for skin cancer (678). The sensitivity and specificity of skin examinations is unknown (679). Total-body skin examinations are safe and may increase the detection of skin lesions, which may be present in unexposed areas. Early detection of skin cancer requires clinical recognition of both precancerous and malignant skin lesions (680). Self-examinations of the skin by patients are probably less accurate than physician examinations (678). Dermatologists have the greatest expertise in correctly identifying premalignant and malignant skin lesions (680).

The American Academy of Dermatology and the National Institutes of Health Consensus Panel recommend regular visits for skin cancer screening and patient education concerning periodic skin self-examinations (681,682). The American Cancer Society recommends monthly self-examinations for all adults and physician skin examinations every 3 yr for individuals between the ages of 20 and 39 yr and annually for individuals >40 yr of age (683). The United States Preventive Services Task Force does not rec-

ommend for or against skin cancer screening for the general population but states that a recommendation may be made to consider referring patients at increased risk for skin cancer to specialists for evaluation and surveillance (678).

Avoiding sun exposure and using protective clothing are recommended for the general population (678). Sunscreens may offer additional protection. It is prudent to make these recommendations to all renal transplant recipients (660). In a recent survey of 122 patients attending a clinic an average of 3.1 yr after renal transplantation, 41% were unable to recall specific skin cancer education and only 14% had ever visited a dermatologist (684).

Anogenital Carcinomas (Table 30)

Definition. Carcinomas of the anogenital region are responsible for substantial morbidity and deaths (646). The most common sites affected by anogenital malignancies reported to the Cincinnati Transplant Tumor Registry include the vulva, anus, perianal region, penis, perineum, and scrotum (646).

Incidence. Carcinomas of the anogenital area represent as much as 2.5 to 2.8% of cancers in the renal transplant population (685,686). Cancers of the female genital tract are the most frequent nonskin cancers in some reports (648). Epidemiologic studies revealed a 100-fold increased risk for cancer of the vulva and anus, compared with the general population (650). Analysis of data from the Australia and New Zealand Dialysis and Transplant Registry demonstrates that, although dialysis patients are not at increased risk for anogenital malignancies, transplant recipients have risks 10 times higher than those of the general population for these malignancies (687). Anogenital malignancies are more common among women than men (2.5:1), in contrast to other neoplasms among transplant recipients, for which men outnumber women (646). The average time between transplantation and the appearance of anogenital malignancies is 114 mo (646). Transplant recipients are generally much younger (41 yr) when anogenital cancers

Table 30. Anogenital carcinomas

Incidence	Anogenital cancers make up 2.5 to 2.8% of cancers among transplant recipients. The risk of anogenital malignancies is 10-fold higher among renal transplant recipients than in the general population, and the risk of cancer of the vulva and anus has been reported to be 100-fold higher.
Consequences	Multiple and extensive lesions are common. Some patients experience a field effect, with involvement not only of the anogenital area but also of the uterine cervix, vagina, or urethra. Destructive lesions and metastases may require radical surgery, chemotherapy, radiation therapy, and loss of the allograft because of reduction/discontinuation of immunosuppressive therapy. Approximately 11% of patients die as a result of their malignant neoplasms.
Rationale	The incidence of anogenital lesions is high, and the clinical presentation is often misleading. Regular surveillance with biopsies is necessary to determine the presence of dysplasia or malignant transformation. Lesions identified early can be successfully treated, but extensive disease may be refractory to therapy.
Recommendations	Yearly physical examinations of the anogenital area, including pelvic examinations and cytologic studies for women, are recommended (A). Follow-up surveillance, with biopsies of lesions and prompt treatment of warts, is recommended (A). There are insufficient data to recommend for or against anoscopy and biopsies of the anal epithelium as screening techniques (C).

are diagnosed, compared with patients in the general population, who are generally 50 to 70 yr of age when cancers are diagnosed (646,688). Carcinoma of the vulva and perineum is the fourth most common tumor among children who have undergone transplantation, representing approximately 4% of all neoplasms in this group (659). Pediatric renal transplant recipients present with anogenital malignancies at an average age of 27 yr (659).

Immunosuppression and oncogenic viruses seem to be important in the pathogenesis of anogenital cancer (686). Some anogenital lesions remain refractory to therapy during immunosuppression (689). Renal transplant recipients exhibit a higher incidence of HPV (690), and HPV is associated with anogenital cancers (691). Many transplant recipients have anogenital warts, and transplant recipients with anogenital malignancies commonly have histories of condyloma acuminatum (646,689). Infection with HPV (including oncogenic strains) has been identified in anogenital lesions of renal transplant recipients (689,690). There appears to be an association between the prevalence of HPV DNA and the susceptibility to potentially lethal anogenital squamous cell cancers (692).

Consequences. Although one-third of transplant recipients have *in situ* lesions (646,686), multiple extensive lesions are common (686). Some patients have involvement not only of the anogenital area but also of the uterine cervix, vagina, or urethra by squamous cell carcinoma or severe dysplasia (686). Lymph node extension occurs in at least 11% of patients (686). Treatment may require local excisions, vulvectomies, abdominoperineal resections, and inguinal lymph node resections

(646). Some patients require chemotherapy or radiation therapy (646). In some instances, immunosuppression has been discontinued (689). In a recent report from the Cincinnati Transplant Tumor Registry, 11.6% of transplant recipients with anogenital malignancies died as a result of their malignant neoplasms (646).

Rationale. The incidence of anogenital lesions is high, and the clinical presentation is often misleading. Regular surveillance with biopsies is often necessary to determine the presence of dysplasia or malignant transformation (657). Lesions can be very destructive locally, can be associated with coexistent vaginal and uterine carcinomas, and can cause metastasis and death. Some renal transplant recipients manifest a high susceptibility for the development of potentially lethal malignancies, including anogenital malignancies (692). Neoplastic lesions associated with HPV in immunosuppressed patients have the potential for exceedingly rapid progression (693).

Early diagnosis of anogenital lesions permits early treatment (646). Early lesions can be treated with less destructive methods, whereas extensive disease may be refractory to therapy (689). Lesions that appear clinically benign may be malignant, and lesions that appear to be benign in biopsies may subsequently become malignant (689). Therefore, repeated surveillance, with biopsies of lesions and treatment of condylomas or warts, is recommended (646).

Women should undergo regular pelvic examinations and cytologic studies (686). Women may experience a “field effect,” with multifocal lesions; coexistent uterine cervical carcinomas are observed for up to 17% of patients and vaginal

Table 31. KS and other sarcomas^a

Incidence	The incidence of KS is 0.4% for renal transplant recipients in northern and western countries but is as high as 4 to 5% for Arab, Jewish, or Mediterranean patients. KS represents 3 to 4% of all tumors in transplant recipients reported to large transplant registries, but it accounts for up to 70% of all <i>de novo</i> tumors reported after renal transplantation in Saudi Arabia. Sarcomas (other than KS) are also observed with increased frequency among transplant recipients and represent 1.7% of neoplasms reported to the Cincinnati Transplant Tumor Registry.
Consequences	Patients with KS confined to the skin, conjunctiva, or oropharyngeal mucosa are more likely to experience remissions with therapy than are patients with visceral involvement. Some patients have progressive disease that leads to death. Reduction or discontinuation of immunosuppressive therapy is associated with graft loss in >50% of cases, whereas reinitiation of immunosuppressive therapy leads to recurrence and progression of KS. For patients with visceral involvement, the mortality rate exceeds 50%. Mortality rates for other sarcomas exceed 60%, and up to 20% of patients also have second neoplasms.
Rationale	Renal transplant recipients are at high risk for KS. Complete remissions of KS are much more common when the disease is diagnosed and treated early, before visceral involvement is present. The mortality rate for KS with visceral involvement exceeds 50%, and the rate is close to 100% for patients with disseminated disease involving several organs. Other sarcomas may respond to treatment in the early stages, but metastatic sarcomas are associated with poor survival rates.
Recommendations	Examination of the skin, conjunctiva, and oropharyngeal mucosa should be performed at least yearly. Patients with suspect lesions should undergo biopsies (A). Patients at higher risk because of ethnicity (Arab, Italian, Greek, or Jewish), geographic location (Africa or Middle East), or serologic evidence of human herpes virus 8 infection may benefit from more frequent examinations (B).

^a KS, Kaposi's sarcoma.

carcinomas for 7.6% of patients (646). All women with external anogenital lesions should undergo regular pelvic examinations and cytologic studies (646,686). Anoscopy and biopsies of the anal epithelium can lead to early histologic diagnosis of anal intraepithelial neoplasia and/or anal HPV infection, but further studies are required to determine whether these tests should be recommended as screening tests for renal transplant recipients (690). The optimal frequency of surveillance for anogenital cancer among renal transplant recipients has not been established, but it is prudent to recommend at least annual examinations, with prompt evaluation of any new lesions.

KS and Other Sarcomas (Table 31)

Definitions. KS is rare in the general population and was first described in association with renal transplantation in 1969 (694). KS has also been described in several other clinical settings, including classic KS (in individuals of Mediterranean or Jewish ancestry), endemic KS (in Africa), and epidemic KS (in patients with AIDS) (695). Transplant recipients with KS can present with a combination of nodular and lymphadenopathic forms (696). In the nodular form, reddish-blue to purple nodules or plaques appear on the skin and/or oropharyngeal mucosa. In the lymphadenopathic form, there can be involvement of lymph nodes and the mucosa of the gastrointestinal tract, tracheobronchial tree, and lung parenchyma.

Many other sarcomas have been observed in renal transplant recipients, with the majority involving visceral organs or soft tissues (697). Bone and cartilage involvement by sarcomas in renal transplant recipients is rare (688). The most common varieties of sarcomas (excluding KS) in transplant recipients are fibrous histiocytoma, leiomyosarcoma, fibrosarcoma, rhabdomyosarcoma, hemangiosarcoma, undifferentiated sarcoma, and mesothelioma (697).

Incidence. The incidence of KS is markedly increased among renal transplant recipients, compared with the general population, and ranges from 0.4% for patients in northern and western countries to as high as 4 to 5% for Arab, Jewish, or Mediterranean patients (698,699). The incidence of KS among transplant recipients of Jewish or Mediterranean ancestry may be 500-fold higher than that for the same ethnic groups in the general population (700). KS represents only 0.01 to 0.06% of all tumors in the general population but 3% of tumors reported to the Australian and New Zealand Combined Dialysis and Transplant Registry and 4% of tumors reported to the Cincinnati Transplant Tumor Registry (648,651,701). In Saudi Arabia, KS is responsible for 70% of *de novo* tumors after transplantation (699). On average, KS appears 21 mo after transplantation, with the largest number of tumors being diagnosed within 5 yr after transplantation (695). The male/female ratio for KS among transplant recipients is nearly 3:1 (695).

Several factors seem to be important in the development of KS, including immunosuppression, viral infections, genetic factors, and perhaps environmental factors (695,699). Immunosuppression has been associated with KS, and reduction or discontinuation of immunosuppressive treatment can lead to remissions (701,702). Reinstitution of more intense immunosuppressive therapy is usually followed by recurrence and

progression of KS lesions (701,702). Infection with human herpes virus 8 (HHV-8) has been detected in renal transplant recipients with KS (703–705), and pretransplant HHV-8 seropositivity is a strong risk factor for posttransplant KS (706,707). In a recent case-controlled study, 17 of 25 renal transplant recipients with antibodies to HHV-8 developed KS, compared with 1 of 33 patients with no antibodies to HHV-8 (705). Infection with HHV-8 (or KS-associated herpes virus) could explain the susceptibility of some renal transplant recipients to KS (708). Genetic factors are probably also important, because most transplant recipients with KS are of Arab, Italian, Greek, or Jewish background (705,709). There is an increased frequency of certain MHC phenotypes among patients with KS, but these MHC types correspond to those expected on the basis of the ethnic backgrounds of the affected patients (709). A possible role for environmental factors is suggested by the extremely high incidence of KS among renal transplant recipients in Saudi Arabia (699).

Sarcomas other than KS are also observed more frequently for transplant recipients, compared with the general population; they represent 1.7% of neoplasms reported to the Cincinnati Transplant Tumor Registry, compared with 0.5% in the general population (697). For pediatric organ transplant recipients, sarcomas are the third most common malignancy, comprising 4% of the tumors in children (659).

Consequences. Sixty percent of patients with KS reported to the Cincinnati Transplant Tumor Registry had nonvisceral KS confined to the skin, conjunctiva, or oropharyngeal mucosa (697). Fifty-three percent of these patients experienced complete remissions with treatment, but in some cases the disease progressed even with therapy (697). Most of the deaths in this group were the result of infections or rejection (695,697).

Forty percent of patients with KS reported to the Cincinnati Transplant Tumor Registry exhibited visceral involvement, including the gastrointestinal tract, lungs, lymph nodes, and other organs (65). Skin and oral involvement was also present in most of these cases (697). Only 27% of patients with KS visceral involvement experienced remissions with therapy, and 57% of those patients died in a short time, in most cases as a direct result of KS (695,697). A report from a single institution that has cared for large numbers of patients with KS also noted high mortality rates for patients with KS involving several organs (699).

Multiple therapies have been used for renal transplant recipients with KS, including changes in immunosuppressive therapy, surgery, radiation therapy, chemotherapy, and immune therapy, among others (697). Reduction/discontinuation of immunosuppressive treatment is usually one of the first therapeutic interventions for KS but can lead to allograft dysfunction and/or irreversible graft loss in more than one-half of renal transplant recipients (695,697). Increasing cumulative doses of immunosuppressive medications used for graft dysfunction or repeat transplantation (even after many years) usually lead to the recurrence of KS and the progression of lesions (701,702).

Transplant recipients with KS frequently have other malignancies, and 6% of patients reported to the Cincinnati Transplant Tumor Registry exhibited a second primary malignancy

(697). KS is a less common tumor in the pediatric transplant population but is associated with a very high mortality rate for children with visceral KS (659).

Sarcomas (other than KS) are associated with high morbidity and mortality rates for transplant recipients, with at least 61% of transplant recipients with other sarcomas in the Cincinnati Transplant Tumor Registry being reported as dead, in most cases (44%) as a direct result of the sarcomas (697). A relatively large number of sarcomas (6%) occur adjacent to or in the renal allograft itself (697). Twenty percent of patients with sarcomas also exhibit other neoplasms (697).

Rationale. The detection of reddish-blue macules or plaques in physical examinations of the skin and oropharyngeal mucosa of renal transplant recipients should engender concern regarding KS (695). Cutaneous lesions that appear like infected granulomas that fail to heal are also suspect (695). Histologic examinations of KS lesions typically reveal a mixture of endothelium-lined vascular spaces and spindle-shaped cells (710).

More than 70% of patients with visceral KS also have skin lesions, but some patients do not have skin or oropharyngeal mucosal lesions (695). There are no data in support of or against screening for visceral KS in patients without skin, conjunctival, or oropharyngeal mucosal lesions. Although KS involvement of the gastrointestinal tract can be detected with endoscopy (695) and CT or MRI may reveal pulmonary and visceral involvement (711), these tests are not suitable for routine screening. Abnormalities attributable to pulmonary KS can be noted in chest radiographs (712). Similarly, CT and

MRI may detect other sarcomas (711,713) but are not suitable for routine screening.

Complete remissions from KS are much more common when the disease is diagnosed and treated early, before visceral involvement is present (695,697,701). Once visceral involvement develops, the mortality rate is substantial and exceeds 50% (695,699). Patients with other sarcomas may respond to single or combined treatment modalities, including excision, amputation, radiation therapy, chemotherapy, alteration of immunosuppressive therapy, and administration of interferon, among others. Metastatic sarcoma, even in the general population, is associated with very poor survival rates (714). Early diagnosis of other sarcomas requires attention to any areas of bone abnormalities or soft-tissue swelling, new masses, or unexplained pain.

Posttransplant Lymphoproliferative Disorders (Table 32)

Definition. Posttransplant lymphoproliferative disorders (PTLD) are abnormal proliferations of lymphoid cells that result from immunosuppression (715,716). The increased risk for PTLD and lymphomas after transplantation has been appreciated for more than three decades (656,717,718). Non-Hodgkin's lymphomas constitute 94% of PTLD (647). Myelomas comprise 4% and Hodgkin's disease 2.5% of the lymphomas reported to the Cincinnati Transplant Tumor Registry (647). Studies of non-Hodgkin's lymphomas occurring after transplantation revealed that 87% arise from B lymphocytes, 13% are of T cell origin, and <0.5% are of null cell

Table 32. Posttransplant lymphoproliferative disorders^a

Incidence	Lymphomas occur in 1 to 5% of renal transplant recipients. The incidence is highest in the first 1 yr to after transplantation, with PTLD being reported for 0.2% of patients during the first 1 yr. Thereafter, the incidence of lymphomas stabilizes at approximately 0.04%/yr. Lymphomas represent approximately 16% of all tumors observed for adult transplant recipients and >50% of tumors among pediatric transplant recipients.
Consequences	Disseminated disease occurs in many patients. Mortality rates can be as high as 50% for patients with disease developing early after transplantation and as high as 90% for patients with malignant lymphomas that develop several years after transplantation.
Rationale	PTLD carry high morbidity and mortality rates, and patients with early stages of PTLD may respond to reductions or discontinuation of immunosuppressive therapy. Advanced PTLD require aggressive interventions, which are poorly tolerated by immunosuppressed transplant recipients. Clinical responses to therapy are poor for advanced PTLD and lymphomas. Early diagnosis and prompt therapeutic intervention could improve the prognoses for PTLD.
Recommendations	Complete history assessments and physical examinations, with attention to any symptoms suggesting disseminated or localized organ involvement by PTLD, should be performed at least every 3 mo during the first posttransplant year and annually thereafter. Patients at increased risk for PTLD may require more frequent screening (B). There are insufficient data to recommend for or against measuring the EBV viral load in peripheral blood to screen for PTLD among renal transplant recipients (C). There are insufficient data to recommend for or against measuring EBV gene expression in tissue, <i>e.g.</i> , the renal allograft, to screen for PTLD among renal transplant recipients (C). EBV serologic tests, EBV oropharyngeal shedding tests, and serum monoclonal Ig tests are not appropriate screening tests for PTLD (E).

^a PTLD, posttransplant lymphoproliferative disorders; EBV, Epstein-Barr virus.

origin (647). Genetic studies have revealed that most PTLD in solid organ transplant recipients are of recipient B cell origin (719). There is substantial evidence that Epstein-Barr virus (EBV) plays an important role in most PTLD (716,720,721). PTLD can range from benign, polymorphic, polyclonal hyperplasias to highly malignant monoclonal tumors (716,722). PTLD are classified using morphologic characteristics, immunohistochemical analyses, cytogenetic findings, Ig gene rearrangement studies, and EBV clonal studies (716,722–724). There is a strong correlation between morphologic and molecular genetic categories of PTLD and clinical outcomes (723,724).

Incidence. PTLD occur in 1 to 5% of renal transplant recipients (722,725–728). The incidence appears to be higher (up to 10%) for pediatric recipients (727,729). The incidence of PTLD is highest during the first posttransplant year (725). Among 45,141 cadaveric renal transplant recipients from Europe and North America, PTLD occurred in 0.2% during the first 1 yr after kidney transplantation and in 0.04%/yr thereafter (725). Lymphomas represent approximately 16% of all tumors reported to the Cincinnati Transplant Tumor Registry and 11% of the nonskin malignancies in the Australia and New Zealand Dialysis and Transplant Registry (663).

EBV plays a major role in the development of lymphomas after transplantation (720,721,730), and primary infections are associated with the greatest risk (715,721). T cell-mediated immunity controls but does not eradicate EBV infection, which results in clinically latent infection (731). With immunosuppression, the number of EBV-specific cytotoxic T lymphocytes is decreased and there is an increase in the number of circulating EBV-infected B cells. With immunosuppression, EBV-infected B cells can proliferate into polyclonal hyperplasias or even monoclonal lymphomas (715,731). The type and intensity of immunosuppression are important in the development of PTLD, and the use of antilymphocyte antibodies greatly increases the risk (725,732). Other factors, such as MHC mismatching and CMV disease have also been associated with PTLD (663,715). In one pediatric study, Caucasian race and cadaver donor source were identified as risk factors for PTLD (733). The incidence of PTLD among children treated with tacrolimus was substantially higher than that among children treated with CsA (715,733).

Consequences. The clinical presentation of PTLD in transplant recipients is variable, and extranodal involvement is more common than in the general population (715,721). Some patients experience a syndrome similar to infectious mononucleosis, characterized by fever, malaise, and lymphadenopathy, with or without pharyngitis. Some experience a febrile illness with leukopenia and elevations in liver enzyme levels. Others present with focal involvement of the central nervous system, renal allograft, gastrointestinal tract, liver, bone marrow, lungs, or other isolated organs (715,720). Finally, >50% of patients present with disseminated disease affecting multiple organs (647,688,715).

Central nervous system involvement is common among patients with PTLD and was noted in 22% of the cases reported to the Cincinnati Transplant Tumor Registry (734). Central

nervous system lesions frequently involve the brain and are multicentric in distribution (734). The mortality rate associated with central nervous system involvement is extremely high, and only 20% of patients achieve remissions with therapy (734). The allograft itself is involved in up to 20% of patients (688). Renal allograft dysfunction may occur as a consequence of involvement by PTLD (735,736). Gastrointestinal tract involvement is common (737). Presentations may include abdominal pain, gastrointestinal bleeding, obstruction, or bowel perforation (715). Young patients tend to present within the first 1 yr after transplantation and tend to exhibit more diffuse polymorphic lesions, with mortality rates of 38 to 50% (738,739). Older patients present several years after transplantation and exhibit more localized extranodal disease, monomorphic lesions, and mortality rates of 66 to 91% in some series (738,739).

Although some patients achieve complete remissions, overall survival rates may be as low as 36%, with a median survival time of 5 mo (739). Patients with PTLD of T cell origin have very poor prognoses (739). Of 1061 patients in the Cincinnati Transplant Tumor Registry who were treated, 399 (38%) experienced complete remissions (740). Of 1345 treated and untreated patients, 474 (35%) died as a result of PTLD, 216 (16%) died as a result of other causes (but PTLD may have contributed to some of the deaths), and 655 (49%) were still alive (740).

Rationale. Mortality rates exceed 50% for PTLD (715), and symptoms may not occur until late in the disease. Early diagnosis could improve outcomes. Serologic evidence of EBV infection or reactivation is not reliable for immunosuppressed transplant recipients (715). Viral reactivation and excretion may occur without changes in antibody titers (721,741). Measurements of the EBV burden in the peripheral blood may be useful for identifying patients who will eventually develop PTLD (742–744). Although an early study noted that the detection of EBV genomic material in circulating B cells was not predictive of lymphoma development (745), subsequent studies demonstrated that the results of semiquantitative and quantitative PCR assays for EBV DNA in peripheral blood were correlated with the risk of developing PTLD (743,744,746). However, the utility of measuring the EBV viral load to screen for PTLD has not been systematically evaluated.

Determination of oropharyngeal shedding of EBV does not appear to be useful for the identification of transplant recipients at risk for EBV-associated morbidity (741). Quantitative oropharyngeal EBV shedding, as determined using molecular probes, is almost universally observed for seropositive renal transplant recipients in the first posttransplant year. Many allograft recipients who shed very high levels of EBV in the oropharynx do not subsequently develop clinically apparent PTLD (741).

In a study of liver transplant recipients that used *in situ* hybridization for detection of the *EBER1* gene during latent EBV infection, it was noted that expression of this gene in liver tissue preceded the occurrence of PTLD (747). However, others failed to confirm the association of EBV gene expression in

liver tissue with subsequent progression to PTLD (748). Therefore, additional studies are needed to determine whether organ-specific diagnoses of EBV can be used to screen for PTLD.

Sonography (749), CT (750,751), and MRI (752–756) are useful in diagnosing PTLD but have little benefit for routine screening of asymptomatic patients. Upper and lower endoscopic evaluation of the gastrointestinal tract is the diagnostic procedure of choice for early recognition of abnormal lesions involving the bowel and for obtaining biopsy samples to establish the diagnosis of PTLD (757). Involvement of the gastrointestinal tract by PTLD is common, but symptoms may not occur until late in the disease (757). There are no data for or against routine endoscopic evaluation of the gastrointestinal tract in asymptomatic renal transplant recipients as a screening test for PTLD. Renal transplant recipients with unexplained gastrointestinal manifestations should be promptly referred for endoscopic evaluation of the gastrointestinal tract.

Uroepithelial Malignancies and Renal Carcinomas (Table 33)

Definition. Renal carcinomas reported to the Cincinnati Transplant Tumor Registry include renal cell carcinomas (74%), transitional cell carcinomas/urothelial carcinomas (12%), and miscellaneous carcinomas (14%) (647). Most renal carcinomas occur in the native kidneys, but renal cell carcinomas have been accidentally transplanted with allografts (758). Renal cell carcinoma has also been reported to develop in renal allografts many years after transplantation (759).

Incidence. Renal carcinoma occurs in 0.5 to 3.9% of renal transplant recipients (760–762). The risk of renal carcinoma is 10 to 100 times higher for renal transplant recipients than for the general population (648,761). Several risk factors have been associated with renal carcinoma in renal transplant recipients, including previous analgesic abuse, previous history of renal cell carcinoma, and acquired renal cystic disease (758,762–764). Analgesic abuse is associated with an increased risk for urothelial cancers, specifically tumors of the renal pelvis and the bladder (763). In one study, urothelial

tumors were reported for 17% of patients who received renal transplants because of analgesic nephropathy, compared with only 0.1% of patients who received transplants because of other causes of ESRD (763). Data from the Cincinnati Transplant Tumor Registry indicated that patients with prior histories of symptomatic renal carcinomas who underwent renal transplantation after surgical removal of their lesions experienced a 25% rate of recurrence of renal cell carcinoma. More than one-half of the renal carcinoma recurrences occurred during the first 2 yr after renal transplantation (758). Acquired renal cysts occur in 40 to 80% of patients who undergo long-term dialysis (764,765), and acquired cysts are an important risk factor for the development of renal cell carcinomas among dialysis patients (762,764). A longer duration of hemodialysis before transplantation, male gender, and older age are associated with acquired renal cystic disease and the development of renal carcinoma after renal transplantation.

Consequences. Renal transplant recipients with renal cell carcinomas may present with fever, weight loss, early satiety, anorexia, and hematuria, among other manifestations (765). However, many patients do not present with symptoms or abnormal findings until their disease is advanced. Renal carcinomas can be particularly aggressive in some renal transplant recipients (765). Many patients exhibit widespread metastases involving the lymph nodes, liver, and lungs, as well as invasion of the renal veins and inferior vena cava. Approximately 40% of transplant recipients with renal cell carcinomas die as a consequence of their malignancies (758). The clinical course of urothelial tumors is particularly aggressive. More than one-half of the patients with urothelial cancers already have extensive disease at the time of presentation, and the median survival time for this group is only 17 mo (763). In contrast, 24% of renal cell carcinomas in the Cincinnati Transplant Tumor Registry were discovered incidentally (740).

Rationale. Most renal transplant recipients exhibit no clinical manifestations early in the course of renal carcinomas. Surgical resection at an early stage is the only established cure for renal carcinomas. The course of renal tumors appears to be

Table 33. Uroepithelial malignancies and renal carcinomas

Incidence	Renal carcinomas occur in 0.5 to 3.9% of renal transplant recipients. The risk of renal carcinomas among renal transplant recipients is 10 to 100 times higher than that in the general population. Renal carcinomas represent approximately 3.6% of all tumors observed in transplant recipients.
Consequences	Renal carcinomas are aggressive in renal transplant recipients. Widespread metastasis to the lymph nodes, liver, and lungs and invasion of the renal veins and inferior vena cava can occur. Approximately 40% of transplant patients with renal cell carcinoma die as a result of their malignancies. Patients with uroepithelial tumors usually present with metastatic disease and have a median survival time of only 17 mo.
Rationale	Early clinical manifestations are usually absent for renal carcinomas. The course is aggressive in renal transplant recipients, with local spread and metastases. Good survival rates are possible with early diagnosis and treatment.
Recommendations	Urinalyses and radiographic screening for uroepithelial malignancies and renal carcinoma are not recommended (C). Urine cytologic studies are not recommended for screening for uroepithelial malignancies, except possibly for patients with histories of analgesic abuse (D).

more aggressive in renal transplant recipients than in the dialysis population (765). Tumors grow and metastasize, leading to morbidity and high mortality rates. Disease-free survival rates of >40% for transplant recipients who undergo successful resections of renal carcinomas have been reported to the Cincinnati Transplant Tumor Registry (758). Therefore, early detection of renal carcinomas could improve outcomes.

Urine cytologic analyses are not very useful for detecting urothelial neoplasms that originate in the upper urinary tract (763). An additional limitation in renal transplant recipients is that most urine originates in the transplant kidney and not in the native kidneys (763). Urine cytologic analyses may be useful for detecting lower-tract tumors in patients with histories of analgesic abuse (758). Hematuria, detected by urinalysis for asymptomatic patients, can be caused by renal malignancies, extrarenal malignancies, and nonmalignant disorders (766). The use of urinalyses to screen asymptomatic renal transplant recipients for renal carcinomas has not been evaluated.

Renal sonography may be useful to screen for renal cell carcinomas in renal transplant recipients (760–762,764,767). Renal ultrasonography, however, has limited sensitivity in detecting small masses (750). The optimal frequency for screening has not been established. Several investigators have suggested yearly sonographic examinations for asymptomatic renal transplant recipients (762). Others have recommended twice-yearly sonographic screening for renal transplant recipients at high risk (760) or annual testing for patients with acquired renal cystic disease (764). A study that included repeated sonographic testing revealed a growth rate of 0.5 to 1.0 cm/yr for renal carcinomas in two allograft recipients (762). On the basis of this growth rate of 1 cm/yr and the fact that patients with tumors of <3 cm have limited disease, a group of investigators suggested that ultrasonographic exami-

nations be performed every 3 yr to diagnose renal cell carcinoma of the native kidneys at an early stage (761). There are no prospective data to indicate how cost-effective these screening strategies might be for renal transplant recipients (758).

Contrast-enhanced CT is much more sensitive than sonography for detecting small renal masses (752,762). MRI is at least as effective as contrast-enhanced CT in detecting small renal lesions (752,754). MRI avoids the risk of severe reactions to iodinated contrast material (754). MRI using gadolinium for enhancement does not cause nephrotoxicity (768). Given the sensitivity of CT and MRI for detecting lesions of <1 cm, it could be possible to use these methods as screening tools with less frequent testing, compared with renal sonography. Nevertheless, there are no data for or against the routine use of CT or MRI to screen for renal carcinomas. In the selection of one modality over the other, factors such as the safety of administration of contrast agents, local expertise, and costs should be considered.

Hepatobiliary Carcinomas (Table 34)

Definition. Hepatocellular carcinomas are associated with chronic liver disease, especially chronic hepatitis B virus (HBV) and HCV infections, and are the most important hepatobiliary tumors in renal transplant recipients (647,769).

Incidence. The incidence of hepatocellular carcinoma demonstrates marked geographic variation. The presence of chronic liver disease, especially chronic HBV or HCV infection, greatly increases the risk of hepatocellular carcinoma among renal transplant recipients (647,769). The incidence of hepatocellular carcinoma among renal transplant recipients in Europe is <0.1%, with older male patients exhibiting the highest incidence (655). The incidence of hepatocellular carcinoma is as high as 3% in Taiwan, where there is a very high

Table 34. Hepatobiliary carcinomas

Incidence	The incidence of hepatocellular carcinomas varies by geographic area, from <0.1% to 3%. The risk of hepatocellular carcinoma among transplant recipients is 30 to 100 times higher than that in the general population. Hepatocellular carcinomas represent approximately 1.7% of cancers among transplant recipients but may represent close to 40% of all malignancies observed among renal transplant recipients in some countries.
Consequences	Most patients with hepatocellular carcinomas have advanced disease at the time of presentation and tumors that are unresectable, because of extensive liver involvement, the invasion of hepatic or portal veins, the presence of metastases, or advanced underlying hepatocellular disease. Overall survival rates for patients with hepatocellular carcinoma in the general population are 30% at 1 yr and 5% at 5 yr.
Rationale	Patients with advanced disease exhibit very poor survival rates. Hepatocellular carcinomas grow slowly and may remain confined to the liver. Because tumor stage is the most important predictor of survival rates, early diagnosis could lead to better survival rates. Patients in the general population who undergo surgical resection of small hepatocellular carcinomas exhibit 5-yr survival rates of close to 40%.
Recommendations	Determination of serum α -fetoprotein levels every 6 to 12 mo for patients with liver disease could assist in early detection of hepatocellular carcinomas (C). Performing liver sonography every 6 to 12 mo is currently the most accepted screening method for hepatocellular carcinoma for patients who are considered to be at especially high risk, such as those with chronic hepatitis (C).

incidence of chronic hepatitis associated with HBV and HCV infection (769). The relative risk of hepatocellular carcinoma among renal transplant recipients, compared with the general population, is increased 38-fold in Europe and 100-fold in Taiwan. Hepatocellular carcinomas represent approximately 1.7% of all malignancies reported to the Cincinnati Transplant Tumor Registry (647), and primary liver tumors represent approximately 2% of all malignancies among childhood renal transplant recipients (659).

Consequences. Patients with hepatocellular carcinoma usually present with clinical manifestations late in the course of their disease. Most patients have advanced disease at the time of presentation, which precludes effective therapy. Surgical resection is the only curative treatment for hepatocellular carcinoma, and most tumors are unresectable at the time of presentation (770,771). Most patients survive for only a few weeks or months. Survival rates for patients with hepatocellular carcinoma in the general population are 30% at 1 yr and 5% at 5 yr. Patients who have limited disease and can undergo resection exhibit 5-yr survival rates that range between 25 and 39% (770).

Rationale. Clinical manifestations associated with hepatocellular carcinoma occur only with advanced disease. In nonrenal transplant recipients, hepatocellular carcinomas have been reported to grow slowly and remain confined to the liver for years (770). Because tumor stage is the best predictor of survival, early diagnosis of hepatocellular carcinoma could lead to improvements in outcomes. Patients who undergo surgical resection of small hepatocellular carcinomas exhibit 5-yr survival rates that may approach 40% (770). Screening for hepatocellular carcinoma in nonrenal transplant recipients is controversial (772). Limiting screening to patients at high risk for carcinoma, with a strong likelihood of improvements in life expectancy, has been suggested (772). The indiscriminate application of screening for hepatocellular carcinoma may not benefit most patients with chronic liver disease and cirrhosis (772).

Serum α -fetoprotein can be detected in some patients with early stages of hepatocellular carcinoma (770). The sensitivity of serum α -fetoprotein analyses for the detection of small hepatocellular carcinomas is low (between 20 and 60%) (770,772). Serum α -fetoprotein analyses have high specificity for the detection of hepatocellular carcinoma, exceeding 90% in most series (771,772). False-positive results are caused by the activity of underlying liver diseases (770,771).

Hepatic ultrasonography is a more sensitive test than serum α -fetoprotein measurements for the early diagnosis of hepatocellular carcinoma. The sensitivity of liver sonography exceeds 80 to 85% for the detection of small hepatocellular carcinomas (ranging in size from 1 to 5 cm) (772). The specificity of liver ultrasonography for the detection of liver carcinomas is close to 90% (771). The predictive value of liver sonography could be improved by limiting screening to patients who are at the highest risk for hepatocellular carcinoma, such as those with longstanding hepatitis and chronic liver disease. Unfortunately, the accuracy of sonography is reduced among patients with cirrhosis, because of the presence of cirrhotic nodules (770). Nevertheless, liver sonography performed every 6 mo for patients with longstanding hepatitis and chronic liver disease is currently the most widely accepted screening method for hepatocellular carcinoma.

CT with contrast enhancement is the primary method for detection and characterization of liver lesions (773). The detection of hepatocellular carcinomas in patients with liver cirrhosis is limited because of distorted liver morphologic features and the difficulty of differentiating nodular masses from malignant tumors (770). The use of helical (spiral) CT improves the ability to characterize small hepatic lesions (774). MRI has been reported to have greater diagnostic accuracy for small hepatic lesions, compared with other radiologic techniques (755,770). MRI using newer contrast agents with reticuloendothelial cell specificity, such as supermagnetic iron oxides, may become useful for the detection and characteriza-

Table 35. Carcinomas of the uterine cervix

Incidence	Dysplastic cervical lesions occur in up to 9% of renal transplant recipients, although the incidence may have decreased in recent years. The risk of cervical carcinoma (including <i>in situ</i> lesions) has been estimated to be 3 to 16 times higher for renal transplant recipients than for the general population. Cervical carcinomas represent approximately 3% of all malignancies among transplant recipients.
Consequences	Advanced cervical cancer is associated with poor survival rates in the general population; the 5-yr survival rate is only 14% for patients with advanced disease.
Rationale	Screening for cervical cancer reduces the incidence of invasive cancer and death in the general population. Most cervical neoplasias in transplant recipients respond well to conventional therapy when treated at an early stage.
Recommendations	All women ≥ 18 yr of age and girls < 18 yr of age who are sexually active should undergo pelvic examinations, with Pap smears, annually (A). Screening for human papillomavirus is not recommended for the general population, and there are no convincing data for or against human papillomavirus screening for renal transplant recipients (C). Colposcopy screening for cervical cancer is not recommended (D). Cervicography is not recommended (E).

tion of liver lesions (775). However, there are currently no data on the routine screening of renal transplant recipients for hepatocellular carcinoma using any CT or MRI techniques.

There has been interest in the identification of some other possible serum markers for hepatocellular carcinoma. Lectin-reactive α -fetoprotein, plasma urokinase-type plasminogen activator, serum des- γ -carboxyprothrombin, and prothrombin induced by vitamin K absence or antagonist II are potential serum markers of hepatocellular carcinoma but are not now being used clinically (771).

Carcinomas of the Uterine Cervix (Table 35)

Incidence. Abnormal cytologic features, with dysplastic lesions and cervical intraepithelial neoplasias, have been noted in up to 9% of renal transplant recipients in some studies (776,777). The risk for development of cervical carcinoma has been estimated to be 3 to 16 times higher for renal transplant recipients than for the general population; however, 70% of these patients have *in situ* lesions (685,687,777). The incidence of cervical carcinoma appears to be particularly increased among female patients with functioning grafts before menopause (655). Cervical carcinomas represent approximately 3% of all malignancies among transplant recipients (651). Some recent data suggested that there has been a decrease in the incidence of cervical carcinoma among renal transplant recipients (778).

Several factors have been associated with an increased risk of cervical carcinoma for renal transplant recipients. The number of previous sexual partners has also been identified as a risk factor for cervical carcinoma among renal transplant recipients, similar to observations for the general population (777). The potential contribution of other risk factors for cervical carcinoma that have been noted in the general population has not been determined for renal transplant recipients. The presence of lower anogenital malignancies greatly increases the risk for cervical carcinoma among renal transplant recipients (686).

Consequences. Low-grade cervical neoplasias in renal transplant recipients may respond well to conservative therapies or simple hysterectomies (776). Therapies used for preinvasive lesions include laser vaporization or excision, cryosurgery, cold-knife conization, electrosurgical excision, and simple hysterectomy, among other therapies (779). Advanced-stage disease may not respond even to aggressive therapeutic interventions. In the general population, advanced cervical cancer is associated with a 5-yr survival rate of only 14% (776).

Rationale. There is considerable evidence that regular screening for cervical cancer reduces the incidence of invasive cancer and is associated with reductions in the mortality rate for cervical carcinoma in the general population (776,780). Most cervical neoplasias in transplant recipients respond well to conventional therapy when treated at an early stage (776,781).

Several organizations recommend annual pelvic examinations and Pap smear testing for sexually active women who have reached the age of 18 yr (776,780,782,783). The optimal frequency of Pap smear testing has not been established for the

general population. Women who are undergoing immunosuppression (such as renal transplant recipients) have a higher risk of cervical carcinoma and should undergo pelvic examinations, with Pap smear testing, annually (782). The upper age limit for screening with Pap smear testing is not well established. Although cytologic evaluations of the vagina after total hysterectomy to treat benign disease are generally not recommended (784), it may be prudent to continue periodic testing for renal transplant recipients, because of their higher risk for carcinoma (782).

Regular colposcopic examinations of the cervix have been suggested in some transplant series (785). Colposcopy for detection of suspect lesions in the uterine cervix has poor sensitivity and specificity when used as a screening test for cervical neoplasia among asymptomatic women (776). There is no evidence to recommend for or against routine colposcopic screening for cervical cancer in the general population (776) or among renal transplant recipients. Cervicography has a sensitivity comparable to that of Pap smears but exhibits much lower specificity in the detection of cervical carcinoma (776). Cervicography is not recommended as a screening test for cervical carcinoma in the general population (776). There is no basis to recommend cervicography as a screening test for cervical carcinoma among renal transplant recipients.

Screening for HPV can be performed by visual inspection, Pap smear testing, colposcopy, cervicography, *in situ* DNA hybridization, the dot blot technique, the Southern blot technique, and PCR, among other techniques (786). Several oncogenic strains of HPV (such as types 16 and 18) demonstrate strong epidemiologic associations with cervical cancer. Nevertheless, the positive predictive value of HPV for cervical intraepithelial neoplasia is low (776,778). The incidence of HPV infection among renal transplant recipients is variable (777,778,781). Some authors reported that HPV (especially oncogenic strains) is more common among renal transplant recipients, compared with the general population (787), but others did not (778). Screening for HPV as a screening test for cervical carcinoma is not recommended for the general population (26). There are currently no data for or against HPV screening as a screening test for cervical carcinoma among renal transplant recipients.

Breast Cancer (Table 36)

Incidence. Among malignancies reported to the European Dialysis and Transplant Association–European Renal Association Registry, the breast was the most common cancer location for women, although the incidence of breast cancer was not increased, compared with the general population (655). A recent report on >23,000 female cadaveric renal transplant recipients from North America and Europe noted a breast cancer incidence of 0.3% during the first 1 yr after transplantation. This represented a relative risk of 0.49, compared with the general population (788). The relative risk for breast cancer for these transplant recipients increased to 0.84 in the subsequent years of follow-up monitoring in the study (788). Other groups observed the incidence of breast cancer among female renal transplant recipients to be approximately 0.6%,

Table 36. Breast cancer

Incidence	The incidence of breast cancer among renal transplant patients is 0.3 to 0.6% and is not increased, compared with the general population. The risk of developing breast cancer during the first 1 yr after transplantation is 49% of that for the general population. The risk of breast cancer increases in subsequent years after renal transplantation and that risk is between 0.84 and 1.3, compared with the general population. Breast cancers represent approximately 3% of all malignancies among transplant recipients.
Consequences	Breast cancer is the leading cause of cancer-related deaths among females 15 to 54 yr of age in the general population. More than one-half of all deaths resulting from breast cancer are among women who are ≥ 65 yr of age. Breast cancer causes local tissue destruction and extension, as well as widespread metastasis, including extension to the lymph nodes, lungs, bones, liver, and central nervous system. Therapies for breast cancer can be associated with significant morbidity. Renal transplant recipients with advanced breast cancer also have very poor prognoses.
Rationale	Screening reduces the mortality rate associated with breast cancer in the general population. Smaller tumors that have not metastasized have much better prognoses than do cancers that are in more advanced stages.
Recommendations	<p>Women 50 to 69 yr of age should undergo screening mammography every 1 to 2 yr, with or without clinical breast examinations (A).</p> <p>Women 40 to 49 yr of age may opt to undergo screening mammography every 1 to 2 yr, with or without clinical breast examinations, but evidence regarding the benefit of screening at this age is conflicting (C).</p> <p>Women ≥ 70 yr of age, with reasonable life expectancies, may opt to undergo screening mammography every 1 to 2 yr, with or without clinical breast examinations, but there is little evidence for or against screening at this age (C).</p> <p>Women < 50 yr of age who are at high risk (<i>e.g.</i>, family history of premenopausal breast cancer in a first-degree relative or prior history of breast and/or gynecologic cancers) should undergo screening mammography every 1 to 2 yr, with or without clinical breast examinations, although there are few data for or against screening in this population (C).</p>

and relative risks for breast cancer have been noted to be as high as 1.1 to 1.3, compared with the general population (648,685,788).

Breast cancer represents approximately 3% of all malignancies reported to the Cincinnati Transplant Tumor Registry and approximately 5% of the nonskin cancers reported to the Australia and New Zealand Combined Dialysis and Transplant Registry (647,663). In the United States, the lifetime risk for women to develop breast cancer is approximately 1 in 8 (789). The estimated lifetime risk for women to die as a result of breast cancer is approximately 3.6% (790). Several explanations have been proposed for the lower incidence of breast cancer shortly after renal transplantation. It has been suggested that immunosuppression during a premalignant phase in breast neoplasia may reduce the incidence of subsequent development of breast cancer (791). Other groups have suggested that the lower incidence of breast cancer noted early after renal transplantation may be a direct consequence of increased examinations and screening before renal transplantation (788).

Consequences. Breast cancer is associated with high morbidity and mortality rates. In the general population, breast cancer is the leading contributor to cancer-related deaths for female patients in the 15- to 54-yr age group (790). The incidence of breast cancer increases with age, and more than one-half of all deaths attributable to breast cancer occur in women ≥ 65 yr of age (790). Breast cancer advances by local

extension and also by metastasis to multiple sites, including the lymph nodes, bone, lungs, liver, and central nervous system, among other sites (792). Treatments include surgery, radiation therapy, chemotherapy, and hormonal therapy. Extensive disease is not curable with conventional therapy, and interventions are usually limited to palliation of symptoms (792). Renal transplant recipients with advanced breast carcinoma have very poor prognoses (793).

Rationale. Randomized controlled trials in the general population have demonstrated that screening reduces the mortality rate for breast cancer (789,790). Screening mammography is associated with 20 to 30% reductions in the mortality rate for women 50 to 69 yr of age (789,790). Screening mammography for women 40 to 49 yr of age also reduces the mortality rate, and the effect is statistically significant 15 yr after the beginning of screening (789,794). Renal transplant recipients may develop aggressive breast cancer, and there is no reason to think that screening for breast cancer would not reduce the mortality rate for this population as well.

Breast self-examinations have limited sensitivity for the detection of breast carcinoma (790). Breast self-examinations are considered a supplement to but not a substitute for other screening tools available for the detection of breast carcinoma (789). Clinical breast examinations are useful for the detection of breast cancer when they are performed in addition to mammography (789). Some palpable breast cancers may not be

visible in mammograms and may be detected early only in breast examinations (789).

The best test for the early detection of breast cancer is x-ray mammography. The sensitivity of mammography alone as a screening test for breast cancer is approximately 75%, and the sensitivity increases to 88% when mammography is used in combination with clinical breast examinations (790). The development of more advanced techniques for mammography has improved its sensitivity and specificity for the detection of breast carcinoma. There is a risk of false-positive results with breast cancer screening (790). A significant proportion of women without breast cancer require additional evaluation because of abnormal breast cancer screening test results (795).

Women with family histories of premenopausal breast cancer in a first-degree relative (brother, sister, or parent) and women with histories of breast and/or gynecologic cancers are at high risk for breast cancer. It is logical that such women warrant more aggressive screening, although there are few data to substantiate this. Several organizations have made detailed recommendations regarding screening for breast cancer (789,790,794). Applying these guidelines to the screening of women after renal transplantation seems to be prudent, although there have been no studies evaluating the effects of breast cancer screening in this population.

Colorectal Carcinomas (Table 37)

Definition. Adenocarcinomas constitute the majority of colorectal malignancies.

Incidence. Carcinomas of the colon and rectum occur in up to 0.7% of renal transplant recipients, with risks ranging from two- to threefold higher than those for the general population (685). Data from the EDTA-ERA Registry indicate that the incidence of colon cancer is not increased in the first 10 yr after renal transplantation. Nevertheless, after the first 10 yr after renal transplantation, there is a two- to fourfold increase in the risk of colon cancer for male and female renal transplant

recipients (655). The incidence of carcinomas of the rectum does not seem to be increased among the renal transplant recipients monitored in the EDTA-ERA Registry. A recent report of a large number of transplant recipients also noted an increase in the incidence of colon cancer but a reduction in the incidence of rectal cancer among transplant recipients, compared with the general population (796). Carcinomas of the colon and rectum represent approximately 3.6% of the malignancies among transplant recipients reported to the Cincinnati Transplant Tumor Registry (647).

Consequences. Colorectal cancer is the second most common form of cancer in the general population in the United States, and it exhibits the second highest mortality rate (797). The lifetime risk of dying as a result of colorectal cancer for an individual in the United States is approximately 2.6% (797). Colon and rectal carcinomas can present with bleeding, abdominal pain, changes in bowel habits, or other manifestations. Cancers of the colon may spread directly from the bowel to regional lymph nodes and through the portal circulation to the liver. Metastases to the peritoneal cavity, lungs, and other distant sites can also occur (798). Renal transplant recipients with metastatic colon carcinomas have very poor prognoses (793). In some studies, the prognoses for renal transplant recipients with colorectal cancers appear to be similar to those for individuals in the general population with the same diagnosis (655).

Rationale. The estimated 5-yr survival rate for patients in the general population with localized colorectal carcinoma is 91%, but the rate decreases to <6% for patients with metastatic disease (797). Screening for colorectal carcinoma in the general population has been demonstrated to lead to the diagnosis of lesions that are smaller and more localized (799). Screening for rectal carcinoma using fecal occult blood testing and sigmoidoscopy has been demonstrated to lead to reductions in colorectal cancer-associated mortality rates. There are groups of individuals, such as those with some hereditary conditions,

Table 37. Colorectal carcinomas

Incidence	Colorectal carcinomas occur in up to 0.7% of renal transplant recipients. Although the incidence of colorectal carcinoma is not increased in the first few years after renal transplantation, it is increased by two- to fourfold, compared with the general population, after 10 yr. Colorectal carcinomas represent approximately 3.6% of malignancies among transplant recipients.
Consequences	Colorectal carcinoma can present with diverse symptoms, including bleeding, pain, weight loss, and changes in bowel habits. Extension can occur directly through the bowel into the regional lymph nodes, peritoneal cavity, and liver. Metastasis to distant locations can also develop. The estimated 5-yr survival rate for metastatic colorectal cancer in the general population is only 6%.
Rationale	Screening for colorectal cancer is associated with reductions in mortality rates for colorectal cancer. Renal transplant recipients appear to exhibit a higher incidence of colorectal cancer. The prognosis for early-diagnosed colorectal cancer in renal transplant recipients appears to be similar to that for individuals in the general population.
Recommendations	Renal transplant recipients who are ≥ 50 yr of age should undergo screening for colorectal cancer with annual fecal occult blood testing and flexible sigmoidoscopy performed every 5 yr (A). Patients who are at higher risk for colorectal carcinoma may need more frequent screening for colorectal carcinoma (A). Digital rectal examinations are insufficient as a screening test for colorectal carcinoma (E).

personal or family histories of other cancers, or inflammatory bowel disorders, who are at higher risk for colorectal carcinoma and benefit from screening for colorectal cancer (799). Renal transplant recipients may experience a higher incidence of colorectal carcinomas and should benefit from screening.

The digital rectal examination is of limited value as a screening test for colorectal cancer. Fewer than 10% of colorectal cancers can be palpated by the examining finger (797). Annual fecal occult blood testing for asymptomatic individuals decreases the mortality rate for colorectal cancer (797,799,800). The sensitivity and specificity of fecal occult blood testing for the detection of colorectal cancer in asymptomatic individuals are influenced by the protocols for collecting and testing samples (800,801). Flexible sigmoidoscopic screening of asymptomatic individuals has also been associated with reductions in the mortality rates for cancer of the rectum and distal colon (797,799,801,802). Sigmoidoscopy with a 60-cm endoscope can detect 65 to 75% of polyps and 40 to 65% of colorectal cancers (801,802).

Barium enema examinations allow observation of the entire colon and are associated with detection of 90 to 95% of polyps of ≥ 1 cm (803). Colonoscopy permits observation of the entire colon and has an estimated sensitivity of 75 to 95% for the detection of lesions within its reach (797). Colonoscopy has been associated with reductions in the incidence of colorectal cancer among cohorts of patients with adenomatous polyps (800). There have been no studies evaluating whether barium enema or colonoscopic examinations reduce mortality rates for individuals of average risk. Costs and potential complications are associated with barium enema and colonoscopic examinations (797,800).

There is no reason to think that evidence-based recommendations for the general population would be any less effective for renal transplant recipients. Guidelines for screening and surveillance for the early detection of colorectal cancer have been developed by the National Cancer Institute, the United States Preventive Services Task Force, the American Cancer

Society, and the American College of Gastroenterology (797,799–801).

Prostate Cancer (Table 38)

Definition. Prostate cancer is now the second most common cause of cancer-related deaths among American men (804). Although it has been underdiagnosed for many years, there has been a recent appreciation of the importance of prostate cancer among renal transplant recipients (805).

Incidence. Prostate cancer is the second most common cause of cancer-related deaths among men in the general population in the United States (806). Prostate cancer has likely been underdiagnosed among male renal transplant recipients. The incidences of prostate cancer among renal transplant recipients range from 0.3 to 1.9% (685,805,807). As the number of older men with functioning renal allografts continues to grow, it is expected that the incidence of prostate cancer will exhibit similar increases. Prostate cancer represents approximately 1.9% of the total number of malignancies reported to the Cincinnati Transplant Tumor Registry (805).

Consequences. Prostate cancer is associated with morbidity and death in the general population. Clinical manifestations include urinary frequency, dysuria, hematuria, and urinary retention. As the disease progresses, local spreading and then metastatic disease, with bone pain and widespread dissemination, occur (807). In the general population, reported 10-yr survival rates for patients with prostate cancer are 75% for patients whose cancers are confined to the prostate, 55% for patients with regional extension, and 15% for patients with distant metastases (804). In a recent report on renal transplant recipients, the mortality rates were 13% for patients with localized prostate cancer at the time of presentation and 33% for patients with metastatic disease at the time of diagnosis. There was a median follow-up period of 33 mo for renal transplant recipients in that study (805).

The treatment modalities that have been used for renal transplant recipients with prostate cancer include radical pros-

Table 38. Prostate cancer

Incidence	The incidence of prostate cancer among renal transplant patients is 0.3 to 1.9%. Prostate cancer has likely been underdiagnosed in the renal transplant population. It is expected that, as the number of older male patients with functioning renal allografts continues to grow, the incidence of prostate cancer will increase.
Consequences	Prostate cancer is associated with urinary symptoms, including hematuria, dysuria, and urinary retention. Bone pain is a manifestation of metastatic disease. The mortality rate for renal transplant recipients with localized prostate cancer is 13%. The mortality rate for transplant recipients who have metastatic disease at the time of diagnosis is 33%.
Rationale	Renal transplant recipients with localized prostate cancer at the time of diagnosis exhibit responses to therapy that are similar to those observed for the general population. Renal transplant recipients with extensive prostate cancer at the time of diagnosis appear to experience rapid disease progression and may present with treatment failures earlier than patients in the general population.
Recommendations	Men at least 50 yr of age who have at least a 10-yr life expectancy should be screened annually with digital rectal examinations and prostate-specific antigen measurements (C). Men at increased risk, <i>e.g.</i> , those with positive family histories of prostate cancer, may benefit from prostate cancer screening starting at a younger age (C).

tatectomy, radiation therapy, and hormonal therapy. Therapeutic limitations include the difficulty of performing pelvic lymph node dissections on the side of the renal allograft. Radiation therapy could also be associated with nephritis and damage to the renal allograft, and shielding of the allograft is recommended.

Rationale. Prostate cancer is one of the most important causes of cancer-related deaths in the general population. Prostate cancers that are localized exhibit better responses to therapy and are associated with lower cancer-related mortality rates than are extensive cancers. In a recent report, it was noted that 84% of renal transplant recipients diagnosed with prostate cancer had localized disease and 16% of patients had metastatic disease at the time their prostate cancers were diagnosed (805). Patients with localized disease exhibited favorable responses to therapy, but patients with advanced metastatic disease exhibited rates of disease progression and treatment failures that appeared to be higher than those in the general population (805).

Digital rectal examinations have been reported to have sensitivities ranging from as low as 18% to as high as 68% for the detection of prostate cancer among asymptomatic men (804). The positive predictive value of digital rectal examinations is higher when the examinations are performed by urologists (804).

Serum prostate-specific antigen testing has a sensitivity of approximately 70% for the detection of prostate cancer among asymptomatic men (806). It is a simple, noninvasive, reproducible test. Several conditions, such as prostatitis and benign prostatic hypertrophy, can lead to elevations in levels. The positive predictive values reported for the measurement of prostate-specific antigen levels as a screening test for prostate cancer range between 26 and 52% (804). The prostate-specific antigen test appears to be valid for the early detection of prostate cancer after renal transplantation (808).

Transrectal ultrasonography has a reported sensitivity of 57 to 68% for the detection of prostate cancer among asymptomatic men (804). Transrectal ultrasonography cannot distinguish between benign and malignant nodules and has a lower positive predictive value for prostate cancer, compared with prostate-specific antigen measurements (804). Transrectal ultra-

sonography is usually reserved for patients with digital rectal examination abnormalities and/or elevations in serum prostate-specific antigen levels. Transrectal needle biopsy of the prostate is an invasive test that is reserved for patients with digital rectal examination abnormalities and elevations in prostate-specific antigen levels. It is not an accepted screening test for prostate cancer. CT scanning and MRI are probably not cost-effective screening tests for prostate cancer.

There is no consensus on whether to recommend routine screening for prostate cancer for men in the general population. Several organizations and expert panels have provided different recommendations regarding the potential benefits, risks, and cost-effectiveness of screening for prostate cancer (804,806,809,810). There have been insufficient data to conclusively demonstrate decreases in the mortality rate for prostate cancer as a result of screening (804,806,810). Nevertheless, patients with estimated life expectancies of ≥ 10 yr may benefit from screening (809).

Given the potential effects of prostate cancer among renal transplant recipients, it seems prudent to screen for prostate cancer, using digital rectal examinations and prostate-specific antigen measurements, yearly starting at age 50 yr for men whose life expectancy is ≥ 10 yr. It is also reasonable to initiate screening at an earlier age (such as 40 yr) for men with special risk factors, such as black race and family histories of prostate cancer. Physicians and health care professionals should discuss with each patient the potential benefits and limitations of the screening, diagnosis, and treatments for prostate cancer before screening is initiated (810).

Lung Cancer (Table 39)

Definition. Lung cancer is a leading cause of cancer-related deaths for both men and women in the United States. It is associated with very poor prognoses.

Incidence. The incidence of lung cancer reported for renal transplant recipients has ranged from $<0.5\%$ to approximately 0.7% in some studies (685,811). In the EDTA-ERA Registry, the lung was the site most commonly affected by cancer in male patients, although the overall incidence of lung cancer was lower among renal transplant recipients than in the general population (655). It was thought that exclusion of smokers with

Table 39. Lung cancer

Incidence	Lung cancer has been reported for $<1\%$ of renal transplant recipients. It represents 5.5% of all malignancies among transplant recipients and up to 9% of all nonskin malignancies in some renal transplant populations.
Consequences	Lung cancer is the leading cause of cancer-related death for men and women in the general population. Five-year survival rates in the general population and for renal transplant recipients with lung cancer are $<15\%$.
Rationale	Lung cancer can be cured only when diagnosed and surgically resected in its early stages. Lung cancer remains asymptomatic in most patients until the disease has advanced, with local extension and metastases.
Recommendations	Patients should be strongly encouraged to refrain from smoking (A). Screening for lung cancer is generally not recommended. Additional studies are needed before screening with low-dose computed tomography can be recommended for high-risk patients (C).

advanced chronic obstructive lung disease from renal transplantation could partly explain these differences (655).

Lung cancers represent approximately 5.5% of all malignancies among organ transplant recipients that were reported to the Cincinnati Transplant Tumor Registry and 9% of nonskin cancers among renal allograft recipients that were reported to the Australia and New Zealand Combined Dialysis and Transplant Registry (647,663). Lung cancers seem to develop at a younger age for transplant recipients, compared with the general population (811). Small cell cancers were also more common in that study (811). Smoking increases the risk of lung cancer among renal transplant recipients (812).

Consequences. Patients with lung cancer usually present with symptoms related to involvement of the respiratory tract (813). Metastases to distant sites and paraneoplastic syndromes also develop in many patients (813). Cancer of the lung is the leading cause of cancer-related deaths for men and women in the United States. The 5-yr survival rate for patients with lung cancer in the general population is <13% (814). Renal transplant recipients in the EDTA-ERA Registry who developed lung cancer exhibited a 5-yr survival rate of <15% (655).

Rationale. Lung cancer is associated with very high mortality rates for the general population and for renal transplant recipients. Lung cancer has one of the poorest prognoses of all cancers and can be cured only when detected and surgically resected in its early stages (814). Lung cancer usually remains asymptomatic until its advanced stages (814). However, screening for lung cancer among asymptomatic individuals, using chest radiographic examinations or sputum cytologic analyses, has not been demonstrated to reduce mortality rates and is not recommended for the general population (814). Chest x-rays have been extensively studied as a screening test for lung cancer in the general population. By the time lung cancer is indicated in chest x-rays, metastatic dissemination

has often occurred, which limits the effectiveness of chest x-rays as a tool for the early detection for lung cancer (814). Sputum cytologic analysis has also been studied as a screening test in the general population and appears to be even less effective than chest x-rays. The sensitivity of sputum cytologic analysis for the detection of lung cancer may be as low as 10% (814). A recent study noted that the use of low-radiation dose chest CT for people in the general population at high risk for lung cancer greatly improved the likelihood of detecting lung cancer at an early, potentially curable stage (815). That study led to renewed controversy regarding previous guidelines, which generally recommended against any screening for lung cancer (816,817). Whether low-dose CT may be effective in screening high-risk renal transplant recipients, *e.g.*, cigarette smokers, is unclear.

VIII. Infections

Cytomegalovirus (Table 40)

Incidence. The incidence of CMV disease is generally <5% for recipients who exhibited no prior serologic evidence of CMV (antibodies) [R(-)] and who received kidneys from donors who were also antibody-negative [D(-)] (818). The incidence of primary CMV disease among R(-)/D(+) recipients is approximately 50 to 75% (818). The incidence among R(+)/D(+) or R(+)/D(-) recipients is approximately 25 to 40% (818). The incidence of CMV disease is also influenced by the level of immunosuppressive therapy used. In one prospective study, 37 R(-)/D(-) recipients exhibited no CMV disease, regardless of whether anti-CD3 antibody (Orthoclone OKT3; Ortho Biotech, Raritan, NJ) was used. However, 16 of 45 R(+)/D(±) recipients (36%) developed CMV, and in that group the risk of CMV disease was fivefold greater (odds ratio, 5.2; 95% confidence interval, 1.4 to 17.5) for patients who received OKT3 (819). High doses of other immunosuppressive

Table 40. Cytomegalovirus^a

Incidence	The incidence and severity of CMV infection depend on the presence of latent infection in the donor, the immune status of the recipient, and the amount of immunosuppressive therapy used.
Consequences	CMV results in substantial morbidity and death and may be associated with decreased allograft survival rates.
Rationale	Treating all transplant recipients with CMV prophylaxis is costly, exposes many patients to unnecessary risks of therapy, and may lead to the emergence of resistant strains. It is preferable to select patients that are most likely to develop symptomatic CMV infection for treatment.
Recommendations	Periodic posttransplant screening is recommended as follows: antibody titer assays (E), conventional viral cultures (E), qualitative PCR assays to detect CMV DNA (B), quantitative PCR assays and other methods to quantify CMV DNA (C), rapid culture methods, <i>e.g.</i> , shell vial cultures (C), and methods to detect CMV antigenemia (C). Prophylaxis recommendations are as follows: R(+)/D(+) with antilymphocyte immunosuppression, recommended (A); R(+)/D(+) without antilymphocyte immunosuppression, discretionary (C); R(+)/D(-) with antilymphocyte immunosuppression, recommended (A); R(+)/D(-) without antilymphocyte immunosuppression, discretionary (C); R(-)/D(+) with antilymphocyte immunosuppression, recommended (A); R(-)/D(+) without antilymphocyte immunosuppression, recommended (B); R(-)/D(-) with or without antilymphocyte immunosuppression, not needed (D).

^a CMV, cytomegalovirus; R, recipient; D, donor; -, pretransplant antibody-negative; +, pretransplant antibody-positive.

medications likely also increase the risk for CMV. For example, in the European Mycophenolate Mofetil Cooperative Study, the incidence of CMV was 36% (10 of 28 patients) for patients who received a high dose of MMF (3 g/d), compared with 8% for the 54 patients who received either placebo or 2 g/d MMF (820).

Consequences. CMV also causes considerable morbidity and expense. Acute CMV infection is often manifest as fever, leukopenia, thrombocytopenia, myalgias, and flu-like symptoms. End-organ involvement may cause nephritis, retinitis, hepatitis, gastrointestinal bleeding, and/or pneumonia. CMV may also predispose recipients to other opportunistic superinfections and graft rejection. Indeed, CMV infection is associated with reduced patient and graft survival rates (821). Among 47,146 patients in the UNOS registry, kidneys from CMV-positive donors demonstrated approximately 4% lower graft survival rates at 3 yr, compared with kidneys from CMV-negative donors (822).

Rationale. The prevention of CMV remains a major goal in kidney transplantation, and guidelines have been developed for CMV prophylaxis in the early posttransplant period (818). In theory, screening should reliably identify patients destined to develop symptomatic CMV, thereby allowing the selective use of antiviral therapy to prevent CMV (823). Selective treatment of high-risk patients, rather than indiscriminate treatment of all transplant recipients, could reduce cost, avoid adverse drug reactions, and help prevent the emergence of resistant CMV strains (824). Antibody titers are useful in assessing the risk of CMV infection at the time of transplantation, by establishing whether the donor and/or recipient were previously infected with CMV. Antibody titers and traditional viral cultures are useful for diagnosing CMV infection after its development but do not change quickly enough to be used to screen for impending CMV infection (825,826).

The use of a monoclonal antibody against CMV early antigen in a shell vial culture assay was developed for rapid detection of CMV viremia. However, this assay was supplanted by assays using antibodies against viral immunodom-

inant matrix protein pp65 (detected in peripheral blood leukocytes), which not only is more rapid but also is quantitative (825,827). For example, in a prospective study of 64 patients, CMV pp65 antigenemia testing exhibited a sensitivity of 87.5% and a specificity of 92.5% and detected antigenemia 8 d before the onset of symptoms (825). Recently, flow cytometry has been used to quantify the number of pp65-positive cells in peripheral blood and thereby detect early antigenemia (828).

PCR techniques to detect CMV DNA in blood are extremely sensitive (829–832). The PCR assay has been further enhanced by reverse transcription and other techniques that quantify CMV RNA and distinguish latent from active infection. The nearly 100% sensitivity and specificity of PCR assays using leukocytes made it possible to detect CMV in the blood 8 to 13 d before the onset of symptoms for 37 recipients who were seronegative at the time of transplantation (829). These assays were less predictive for recipients who were seropositive at the time of transplantation (829). Non-PCR methods are very specific but are not quite as sensitive as PCR for the detection of viremia before the onset of symptoms (829).

Therefore, techniques that use specific monoclonal antibodies against CMV and techniques that quantify CMV DNA levels in peripheral blood leukocytes appear to be sensitive and specific. However, they have not yet been compared in large prospective trials that accurately assess their positive and negative predictive values for populations with different risks for CMV. In addition, whether these tests will be cost-effective in identifying patients for preemptive therapy has not been adequately studied. In short, there are currently insufficient data to justify the widespread clinical application of any posttransplant CMV screening.

Chemoprophylaxis for CMV has been demonstrated to be effective in large, randomized, controlled trials. Agents that have been studied include acyclovir, ganciclovir, valacyclovir, and intravenously administered Ig. Chemoprophylaxis should be used according to the risk for CMV, as recommended by existing guidelines (818).

Table 41. Influenza A and B

Incidence	The incidence is unknown but is likely at least as high as in the general population.
Consequences	Influenza is a potentially fatal infection in immunocompromised patients. It is also associated with substantial morbidity and cost.
Rationale	Most patients respond to vaccination, although the proportion of patients who exhibit adequate antibody responses is lower, compared with normal subjects. Vaccination does not appear to cause acute rejection or other major adverse effects among renal transplant recipients.
Recommendations	Transplant recipients should receive annual influenza vaccinations (October to November) (A). Health care workers with close contact with renal transplant recipients should also receive annual influenza vaccinations, to protect themselves and their patients (A). Prophylactic amantadine, rimantadine, zanamivir, or oseltamivir treatment should be considered for renal transplant patients who are not yet vaccinated or who are not expected to exhibit an antibody response to vaccination because of high doses of immunosuppressive medications. Chemoprophylaxis should be administered only during periods of influenza activity (B). During outbreaks of influenza, transplant recipients should be monitored closely and considered for antiviral therapy initiated during the first 48 h of symptoms (B).

Influenza A and B (Table 41)

Incidence. Few studies have reported the incidence of influenza among renal transplant recipients, but there is no reason to think that the incidence is less than that in the general population and there are many reasons to suspect that it may be higher. The level of immunosuppressive therapy that patients receive may increase the risk for influenza. In one study of 54 patients who received antilymphocyte antibody therapy, 2 subsequently developed influenza (833).

Consequences. It is likely that influenza is more severe when it occurs among immunosuppressed renal transplant recipients, although systematic studies documenting this finding are lacking. Influenza can be fatal. Bacterial superinfections are common. In a study of 12 pediatric organ transplant recipients with influenza B (5 of whom were kidney recipients), 5 exhibited neurologic involvement and 1 died; 10 were hospitalized and 2 required mechanical ventilation (834).

Rationale. It is likely (albeit unproven) that influenza infection is at least as common and probably more severe among renal transplant recipients, compared with the general population. For the general population, studies have clearly demonstrated that influenza vaccination reduces infection and its consequences (835). Several studies examined the safety and efficacy (based on increases in antibody titers) of influenza vaccination among adult and pediatric renal transplant recipients. Most studies reported that 50 to 100% of the recipients responded to vaccination. The response rate was often less than that of control subjects but was nevertheless adequate to justify the use of vaccination for renal transplant recipients (836–847). In one study, no benefit of a second dose was observed (848). In most of the studies, the numbers of patients were too small to reliably indicate whether some patients were more likely to respond than others. However, one study reported that patients receiving CsA were less likely to respond than patients receiving azathioprine (840), and another study reported that patients with decreased renal function were less likely to respond (846). In none of the studies was there an increase in acute rejections or other major adverse effects. Data on the efficacy of vaccination in studies including other organ transplant recipients corroborate the efficacy and safety of vaccination (848–854). One study of 68 (kidney and other) organ transplant recipients confirmed that a second or third injection did not increase the response rate (848). In a recent survey of pediatric renal transplant centers, almost 90% recommended influenza vaccination (855).

A recent randomized controlled trial among 20 hospitals demonstrated that offering influenza vaccinations to health care workers increased the rate of vaccination from 4.9% in control sites to 50.9% in treatment sites (856). In hospitals where health care workers received vaccinations, the mortality rate among patients was significantly reduced (856). A similar trial also reported reduced mortality rates with the vaccination of health care workers (857). Therefore, it is reasonable to conclude that the vaccination of health care workers who are in close contact with renal transplant recipients may reduce the incidence of influenza-related morbidity and death not only

among the health care workers but also among the patients for whom they care.

Amantadine and rimantadine hydrochloride are approximately 70 to 90% effective against influenza A in the general population. Neither is effective against influenza B, and neither should be considered a substitute for vaccination (858). Rimantadine appears to be associated with fewer central nervous system side effects than amantadine, but it is more expensive. These drugs may also be effective when administered within 48 h after illness onset and can reduce the severity and duration of symptoms without inhibiting the development of immunity. A recent randomized controlled trial also demonstrated that the neuraminidase inhibitor zanamivir is efficacious and well tolerated for the prevention of influenza in the general population (859). Zanamivir, administered once daily by inhalation, has the advantage of being effective against both influenza A and B. Like amantadine and rimantadine, zanamivir can also reduce the duration and severity of illness if therapy is initiated early (within 36 to 48 h) after the onset of symptoms (860–862). A 5-d course of zanamivir therapy was also effective in preventing infection among patients with presumed exposure to influenza in the community (863–865). Finally, in two randomized controlled trials, a 6-wk course of oseltamivir (an oral neuraminidase inhibitor that is active against influenza A and B) therapy was effective in preventing influenza in the community (866). Oseltamivir was also effective if administered within 36 h after the onset of influenza symptoms (867) or after experimental influenza A inoculation (868). None of the four antiviral agents discussed above has been demonstrated to prevent serious influenza-related complications.

The Advisory Committee on Immunization Practices recommends that amantadine or rimantadine be considered for patients at high risk who are vaccinated after influenza activity has begun and that therapy be continued for approximately 2 wk, until immunity has developed (858). (In the United States, zanamivir and oseltamivir are currently licensed for treatment but not for prophylaxis.) Chemoprophylaxis should also be considered for patients who cannot be treated with the influenza vaccine, *e.g.*, patients with histories of egg allergies and individuals at high risk (including patients receiving immunosuppressive medications) who are expected to exhibit an inadequate antibody response to influenza vaccine. Chemoprophylaxis should be administered only during the influenza season. There are no data for renal transplant recipients to suggest which patients should receive chemoprophylaxis. A reasonable strategy would be to limit the use of amantadine, rimantadine, zanamivir, or oseltamivir to the influenza season and to patients who have not yet been vaccinated or are receiving high doses of immunosuppressive medications, *i.e.*, patients who may not develop immunity despite vaccination (858). The inappropriate use of antiviral agents could contribute to the emergence of resistant strains and should be discouraged (869). Effective timing of the use of neuraminidase inhibitors requires physicians to be aware of outbreaks of influenza in their communities. This information is reported by the Centers for Disease Control and Prevention and is updated weekly (<http://www.cdc.gov/ncidod/diseases/flu/fluvirus.htm>).

Table 42. Tuberculosis^a

Incidence	The incidence of TB among renal transplant recipients is higher than that in the general population. The incidence is approximately 1% in North America, but TB is more common in other areas, <i>e.g.</i> , approximately 4%.
Consequences	Substantial morbidity and death.
Rationale	Screening is reasonably effective, and treatment of latent TB infections can prevent potentially fatal complications.
Recommendations	Renal transplant recipients should be considered at increased risk for TB (B). Renal transplant recipients who have not had active TB and who either did not undergo pretransplant screening or were subsequently exposed to TB should be screened with a PPD skin test and a chest x-ray (B). Patients who have never received adequate treatment and who are PPD-positive, have a history of TB, have a chest x-ray suggesting latent TB, have a recent exposure history, or received a kidney from a PPD-positive donor should undergo 6 to 9 mo of therapy with isoniazid (and pyridoxine) (B).

^a TB, tuberculosis; PPD, purified protein derivative.

Tuberculosis (Table 42)

Incidence. Few studies have documented the incidence of tuberculosis (TB) among renal transplant recipients in North America. Among 565 renal allograft recipients in the United States, primary TB developed in 5 (0.9%), whereas none of 14 high-risk patients who were prophylactically treated with isoniazid developed TB (870). In England, a retrospective study reported TB for 11 of 633 renal transplant recipients (1.7%) (871). A similar study in England reported TB for 5 of 400 renal transplant recipients (1.3%) (872). A retrospective study of organ transplant recipients in Spain demonstrated that the incidence of TB was 0.8% (873). Of the 51 cases described, 63% involved pulmonary, 25% disseminated, and 12% extrapulmonary TB. Infection developed at any time after transplantation, but the mean time to diagnosis was 23 mo (range, 15 d to 13 yr). In another study of renal transplant recipients in Spain, 22 of 525 patients (4.2%) with new cases of TB represented a rate of 259/100,000, which was sevenfold greater than the rate of 35/100,000 for the general Spanish population (874). In a retrospective study from South Africa, there were 21 of 487 renal transplant recipients (4.3%) with confirmed TB (875). The median time to diagnosis was 14 mo (range, 2 to 74 mo) (875). In Turkey, TB was reported for 36 of 880 patients (4.1%) (876). A retrospective review from Saudi Arabia reported TB for 14 of 403 renal transplant recipients (3.5%), which yields an annual incidence 50-fold higher than that in the general population (877). Infection appears to be more common after the intensification of immunosuppressive therapy (873,875). Nosocomial outbreaks may also occur in transplant units (878). Transmission of TB with allografts has been reported (879,880).

Consequences. TB is often fatal. In one large retrospective study, 16 of 51 patients (31%) died (873). In another study, 4 of 21 patients (19%) died while receiving active treatment, but only one of these deaths was directly attributable to TB (875). Disseminated disease often involves the liver, spleen, and bone marrow.

Rationale. For the treatment of latent infection to be effective, the risk of active TB should be high, compared with the risk of treatment. There are no adequately powered, randomized, controlled trials among transplant recipients to determine the efficacy of treatment for latent infection. In one double-blind controlled trial from India, 184 patients undergoing dialysis were randomly allocated to receive isoniazid or placebo, and the administration of drug or placebo was continued for 1 yr after transplantation (881). Hepatitis developed in 33 of 92 placebo-treated patients (36%) and in 32 of 92 isoniazid-treated patients (35%). Only 39 of 92 patients (42%) in the placebo-treated group and 34 of 92 patients (37%) in the isoniazid-treated group completed therapy. During the first 1 yr of follow-up monitoring, 7 patients in the isoniazid-treated group and 10 in the placebo-treated group developed TB. However, only three of the patients in the isoniazid-treated group who developed TB had completed treatment. During the second year, four patients in the placebo-treated group and three in the isoniazid-treated group developed TB (881). Because of the large number of patients who failed to complete therapy, the results of this trial were inconclusive. In one retrospective study, there were no cases of TB among high-risk patients who received treatment, but 6 of 27 high-risk patients (22%) who did not receive treatment developed TB (871). In another retrospective study, none of the 14 high-risk patients treated with isoniazid developed TB (870). In a similar study, none of 23 high-risk patients who received isoniazid developed TB, whereas 1 of 13 patients who did not receive isoniazid developed TB (876).

The most common serious adverse effect of isoniazid is hepatotoxicity. The risk of hepatic toxicity attributable to isoniazid is relatively low. In a retrospective study, 126 consecutive renal transplants among 119 patients were prophylactically treated with isoniazid, without screening for the risk of TB (882). Posttransplant hepatitis developed in 13 patients. For only three of these patients was it considered likely that isoniazid caused the hepatitis (882). Nevertheless, the authors

suggested that routine treatment for all transplant recipients was probably not warranted because of the low prevalence of TB and the risk of toxicity from isoniazid. The risk/benefit ratio could be more favorable if isoniazid were administered only to high-risk patients.

Some large, randomized, controlled trials have been conducted with patients immunosuppressed because of HIV infection. In one study of anergic HIV-infected patients, TB was diagnosed in 6 of 257 patients in the placebo-treated group and in 3 of 260 who received isoniazid ($P = 0.30$) (883). In another study of 684 purified protein derivative (PPD)-positive HIV-infected patients, the adjusted TB risk ratio for 6 mo of isoniazid prophylaxis versus placebo treatment was 0.60 (95% confidence interval, 0.23 to 2.76; $P = \text{NS}$) (884). In another randomized controlled study of 118 HIV-infected patients, the relative risk of TB was 3.4 (95% confidence interval, 1.1 to 10.6; $P < 0.05$) for vitamin B6 versus isoniazid plus vitamin B6 (885). Together, these studies suggest that there may be a small benefit of prophylaxis for patients immunosuppressed because of HIV infection. There does not appear to be any advantage in using prophylactic drugs other than isoniazid (886).

In a double-blind, randomized, controlled trial of 617 Chinese men with silicosis (who are at very high risk for TB), chemoprophylaxis significantly reduced the incidence of TB (887). However, the incidence of TB after 5 yr of follow-up monitoring was 27% for the placebo-treated group, *i.e.*, much higher than that reported for transplant recipients. In a study of 7036 veterans in the United States, 63 patients (<1%) developed reactivation TB (888). Nevertheless, isoniazid prophylaxis was significantly better than placebo in preventing reactivation TB among patients who had never received prophylaxis (888). Together, studies in other populations suggest that prophylaxis with isoniazid prevents reactivation TB among high-risk patients. Primary drug resistance is increasingly frequent (889) but is not a reason to avoid using isoniazid.

Guidelines for targeted tuberculin testing and treatment of latent TB were recently developed jointly by the American Thoracic Society and the Centers for Disease Control and Prevention (890). The PPD (Mantoux) skin test involves an intradermal injection of 5 units of tuberculin PPD, with examination of the injection site 48 to 72 h later. The minimal criterion for a positive skin test is a 5-mm-diameter induration for individuals at very high risk (including patients receiving immunosuppressive therapy) (890). The guidelines recommend 9 mo of isoniazid treatment for latent TB (890). However, according to local conditions, a 6-mo rather than a 9-mo course of isoniazid therapy may be acceptable. As an alterna-

tive, a 2-mo course of rifampin and pyrazinamide therapy (based on the results of trials with HIV-infected patients) may be acceptable (891). Active TB should be ruled out, using histories, physical examinations, chest x-rays, and (when indicated) bacteriologic studies, before treatment for latent TB infection is initiated. Patients at risk for liver disease should undergo baseline testing of liver enzyme and serum bilirubin levels. Active hepatitis is a relative contraindication to the use of isoniazid or pyrazinamide. Routine laboratory monitoring during treatment of latent TB infections is indicated for individuals at risk for liver disease (891).

Streptococcus pneumoniae Infections (Table 43)

Incidence. Very few studies have examined the incidence of pneumococcal infections. However, one study found that 14 of 197 renal transplant recipients (7%) developed pneumococcal infections during a 6-yr period (1%/yr) (892). There has recently been an increase in the incidence of penicillin-resistant pneumococcal infections.

Consequences. *S. pneumoniae* infections cause significant morbidity and death.

Rationale. Studies have documented the safety and efficacy of pneumococcal vaccine for renal transplant recipients (893–896). These results have been corroborated by similar studies of heart and liver transplant recipients (850,897,898). For renal transplant recipients, protective antibody titers decrease substantially after 2 yr (895), so revaccination every 2 yr has been recommended.

Pneumocystis carinii Pneumonia (Table 44)

Incidence. Several studies have reported an increase in the incidence of *P. carinii* pneumonia (PCP) among renal transplant recipients. In a retrospective study of 1192 renal transplant recipients who received no PCP prophylaxis, PCP occurred in 3 of 494 patients (0.6%) who received transplants before 1993 and in 7 of 77 patients (9%) who received transplants after 1993 (899). Similarly, the incidence of PCP among renal transplant recipients who received no prophylaxis increased from 1.1% before 1991 to 11.5% in 1991 to 1992 (900). In another study, PCP occurred in 6 of 179 patients (3.4%) between 1977 and 1981 and in 14 of 156 patients (9.0%) after 1981 (901). Treatments for acute rejection and CMV infection increase the risk for PCP (902,903). Greater age has also been associated with increased risk for PCP (900).

Consequences. PCP can cause substantial morbidity and death after renal transplantation.

Rationale. Renal transplant recipients (103 patients) were randomly allocated to receive ciprofloxacin (250 mg daily) or trimethoprim/sulfamethoxazole (TMP/SMZ) (80 mg/400 mg

Table 43. *Streptococcus pneumoniae* infections

Incidence	Approximately 1% of unvaccinated patients/yr.
Consequences	Potentially life-threatening infections and sepsis.
Rationale	Vaccination is safe and efficacious.
Recommendations	Polyvalent pneumococcal vaccine (capsular polysaccharides) should be administered every 2 yr (B).

Table 44. *Pneumocystis carinii* pneumonia

Incidence	Approximately 10% in patients not receiving prophylaxis.
Consequences	<i>Pneumocystis carinii</i> pneumonia causes substantial morbidity and death after renal transplantation.
Rationale	Infection is potentially fatal. Prophylaxis is effective and relatively safe.
Recommendations	Chemoprophylaxis with trimethoprim/sulfamethoxazole is strongly recommended. For patients who cannot tolerate trimethoprim/sulfamethoxazole, dapsone, pentamidine, or atovaquone should be considered (A). Chemoprophylaxis should be used during periods of intensive immunosuppression, <i>e.g.</i> , in the first few weeks after transplantation and during treatment for acute rejection. However, there are insufficient data to recommend the duration and dose of optimal prophylaxis (B).

daily) (904). Although the incidences of urinary tract infections were similar for the two groups, 7 of 51 patients (14%) who received ciprofloxacin developed PCP, whereas none of the patients who received TMP/SMZ developed PCP ($P = 0.006$) (904). These results were corroborated by several retrospective studies that noted dramatic decreases in the incidence of PCP with the institution of routine prophylaxis (900,901,905,906). Patients receiving TMP/SMZ prophylaxis have the added benefit of fewer urinary tract infections (907).

TMP/SMZ is generally safe, although it causes a reversible 15% increase in serum creatinine levels by blocking the tubular secretion of creatinine (908). In a double-blind, randomized, controlled trial, none of the 66 patients who were treated with TMP/SMZ were withdrawn because of an adverse reaction to TMP/SMZ (908). Neither the dose nor the duration of therapy with TMP/SMZ has been systematically investigated for renal transplant recipients. However, a meta-analysis of TMP/SMZ prophylaxis for patients with HIV concluded that low doses were just as effective but were associated with fewer adverse effects, compared with higher doses (909). The dose of TMP/

SMZ should be adjusted for patients with renal insufficiency. TMP/SMZ appears to be the most effective prophylaxis for PCP (909). However, patients who cannot tolerate TMP/SMZ can be treated with dapsone (910). Dapsone occasionally causes methemoglobinemia in renal transplant recipients (911,912). Aerosolized or intravenously administered pentamidine and atovaquone can also be used for PCP prophylaxis (913–915). Aerosolized pentamidine has been reported to cause *torsades de pointes* among renal transplant recipients, and ECG monitoring of therapy has been recommended (916).

Hepatitis B (Table 45)

Incidence. Chronic hepatitis occurs in 5 to 15% of renal transplant recipients, but most cases are associated with HCV infection. A much smaller but poorly defined number of cases are related to infection with HBV.

Consequences. The rate of HBV infection among patients undergoing hemodialysis has decreased significantly in the past two decades, but HBV continues to be responsible for some of the chronic liver disease observed for patients with

Table 45. Hepatitis B^a

Incidence	<5% and probably <2% in North America.
Consequences	Possible adverse effects on patient survival rates.
Rationale	HBV infection in renal transplant recipients is generally acquired before transplantation. Pretransplant vaccination is effective and has reduced the incidence of posttransplant HBV infection. Studies of the general population suggest that patients with active HBV infections benefit from treatment with lamivudine. Small studies suggest that treatment of renal allograft recipients may also be beneficial. The risk of acquiring <i>de novo</i> HBV infection from the allograft, from blood transfusions, or from other sources after transplantation is probably too small to warrant routine screening with expensive serologic tests.
Recommendations	Patients should receive vaccinations for HBV if they do not exhibit serologic evidence of current or prior HBV infection and were not vaccinated before transplantation (A). Previously vaccinated patients who are HBsAg-negative should be tested annually for anti-HBV antibodies and should receive booster vaccinations when the titer decreases to <10 mIU/ml (C). HBsAg-positive transplant recipients should receive lamivudine (100 mg/d) starting at the time of transplantation and continuing for at least 18 to 24 mo (C). Patients who have been adequately screened for HBV before transplantation need not undergo routine serologic screening after transplantation. Aspartate aminotransferase and/or alanine aminotransferase levels are poor markers of viral hepatitis activity and should not be used to screen for hepatitis (D).

^a HBV, hepatitis B virus; HBsAg, HBV surface antigen.

ESRD. For these patients, exposure to HBV could have occurred earlier in life (before the development of renal failure), secondary to nosocomial transmission within the dialysis unit, with perioperative blood product transfusion, or by transplantation of a kidney from an infected donor. Additionally, reactivation of HBV [*i.e.*, re-expression of HBV surface antigen (HBsAg)] after transplantation (917,918) and re-emergence of viral replication in patients with nonreplicative infection (918) have been reported.

The effects of HBV infection on patient and graft survival rates after kidney transplantation remain controversial. Early studies (919,920) reported adverse outcomes among renal allograft recipients with chronic liver disease and HBsAg expression. Subsequent studies demonstrated histologic deterioration for up to 85% of patients, accompanied by increased patient mortality rates (921–926). Interestingly, allograft survival rates were improved in the HBV-positive group in some analyses (927). Many other investigators, however, were unable to detect increases in patient mortality rates in the HBsAg-positive cohort (928–932).

One explanation for the inconsistent results reported from different centers may be related to the number of HBsAg-negative/HBV DNA-positive patients present in each cohort of patients. In one study, 20% of patients who lacked serum HBV DNA expression in baseline analyses exhibited positive results within 12 mo after transplantation (933). Another explanation for the poor outcomes associated with HBsAg positivity could involve coinfection with HCV. Several studies have clearly demonstrated worse prognoses for patients infected with both HBV and HCV (934,935). This finding could be particularly relevant to the poor outcomes reported in many earlier studies, which predated the identification of HCV.

Rationale. Ideally, renal transplant recipients should be vaccinated against HBV before transplantation and even before the onset of ESRD, if possible. Studies have demonstrated that vaccination is less effective after transplantation than before (936–939). Indeed, the antibody response rate to HBV immunization after renal transplantation was observed to be only 9 to 36% (936–939). The Center for Disease Control and Prevention recommends that an increased dose be used for immunosuppressed patients (940), but few data are available for evaluation of the effectiveness of this strategy. How often booster immunizations should be administered to patients with decreasing HBV antibody titers is also not well defined (941). The European Consensus Group of Hepatitis B Immunity has recommended that immunocompromised patients undergo regular testing for anti-HBV antibodies and receive a booster injection when the titer decreases to <10 mIU/ml (942).

Serum transaminase levels have not been observed to be sensitive markers of liver injury and are not well correlated with the extent of histologic liver disease among HBV-infected renal allograft recipients. Furthermore, abnormalities in liver enzyme levels are not specific for HBV infection and could represent damage resulting from drug toxicity or infection with a number of other hepatotropic viruses. Several serologic markers of active or resolved HBV infection are available. HBsAg is the serologic hallmark of HBV infection. Either RIA

or enzyme immunoassays can be used for its detection. HBsAg appears 1 to 10 wk after acute exposure to HBV (943). The disappearance of HBsAg is followed by the appearance of anti-HBV antibodies, thus conferring immunity. In some patients, a “window” period can occur between the clearance of HBsAg and the appearance of anti-HBV antibodies. During this period, identification of IgM antibodies to HBV core antigen may be the only way to establish the diagnosis of acute HBV infection (944). Anti-HBV core antigen antibodies are predominantly of the IgM subclass early in the course of infection and are then mostly of the IgG subclass in patients who recover from acute HBV infection.

HBV e-antigen (HBeAg) is a secretory protein that serves as a marker of active viral replication and infectivity. Its presence is usually accompanied by measurable titers of HBV DNA in the serum. Seroconversion from HBeAg-positive to anti-HBeAg-positive status is generally associated with the clearance of HBV DNA from the serum (945,946). Several molecular assays for the detection of HBV DNA are available (947,948). Hybridization assays are the least sensitive (10^6 viral genome equivalents/liter), followed by branched-chain DNA assays (10^5 viral genome equivalents/liter) and the most sensitive PCR assays (3 to 100 viral genome equivalents/liter).

Although the effects of HBV infection on outcomes after renal transplantation are unclear, a considerable number of studies suggest that, among HBsAg-positive patients, reactivation of quiescent disease (918,933), progression of histologic injury (932), and adverse effects on morbidity and mortality rates in the posttransplant period (921–925) can be observed. Screening for HBV among transplant recipients with unexplained liver dysfunction is justified by recent reports that demonstrated a beneficial effect of lamivudine for HBV-infected renal allograft recipients. Lamivudine is the (–)-enantiomer of 3'-thiacytidine, which is known to be a potent inhibitor of HBV replication (949). Studies with nontransplant patients have demonstrated decreased viral loads, decreased alanine transferase levels, and improved histologic features for patients with chronic HBV infection (950,951). Two small studies demonstrated good responses to treatment with lamivudine (100 mg/d) for renal allograft recipients, with clearance of HBV DNA and normalization of transaminase levels (952,953). Viral replication recurred when therapy was discontinued, and one patient died after developing a viral mutant that exhibited lamivudine resistance (952,953).

Hepatitis C (Table 46)

Incidence. Anti-HCV antibodies have been reported for 10 to 40% of renal transplant recipients (926,954–958). The majority of seropositive patients exhibit circulating HCV RNA in their serum (959).

Consequences. Published reports have failed to generate a consensus regarding the effects of HCV infection on patient and graft survival rates after renal transplantation. Although some centers have observed higher mortality rates for HCV-positive patients (926,960–963), others have not confirmed this finding (959,964,965). Some centers that demonstrated detrimental effects of HCV infection reported an increased risk

Table 46. Hepatitis C^a

Incidence	Ten to 40% of transplant recipients demonstrate antibodies to HCV.
Consequences	HCV infection may be associated with an increased incidence of sepsis and death resulting from liver disease, although this is controversial. Immune complex-mediated glomerular disease of the allograft is associated with HCV.
Rationale	No therapy for HCV has been proven to be safe and effective for renal transplant recipients.
Recommendations	Although screening (and possibly treatment) of HCV is an important part of pretransplant evaluations, routine posttransplant screening is not recommended (D). Chemoprophylaxis for HCV infection is not recommended after transplantation (E).

^a HCV, hepatitis C virus.

of death resulting from sepsis and liver disease for HCV-positive patients, compared with HCV-negative control subjects (926,961–963). Most of those studies were retrospective, with a mean follow-up period of <10 yr. In two studies, however, HCV-positive transplant recipients experienced superior outcomes, compared with patients who continued to undergo dialysis (966,967). A biopsy study clearly demonstrated that some transplant recipients with more advanced chronic hepatitis experienced progression, whereas others with less severe injuries remained in stable condition despite years of immunosuppression (968). Therefore, some of the variance in patient outcomes may be attributable to differences in baseline liver histologic features, which were not thoroughly evaluated in most studies. Interestingly, HCV infection has also been associated with membranoproliferative glomerulonephritis (969–971) and membranous nephropathy (972) in allografts.

Rationale. HCV is the major cause of non-A/non-B hepatitis (973,974). Patients with ESRD are at increased risk for HCV infection because of their continued exposure to blood and blood products, horizontal transmission within hemodialysis units (975), and transmission from infected organ donors (976–978). An increased incidence of acute renal allograft dysfunction is associated with α -interferon treatment among kidney transplant recipients (979–982). Therefore, a better strategy might be to screen and treat HCV with interferon (and possibly ribavirin) before, rather than after, transplantation (983,984).

Although there is a correlation between abnormal liver en-

zyme levels and the presence of histologic liver disease (985), the relationship is weak and serum alanine aminotransferase levels do not generally reflect the degree of liver injury in HCV infection (959,986,987). Indeed, biochemical evidence of liver disease is present in only 40 to 50% of anti-HCV-positive renal transplant recipients (988,989). The measurement of liver enzyme levels as a screening test for HCV infection or as an index of the severity of liver damage in immunosuppressed renal allograft recipients is neither sensitive nor specific enough to be recommended for routine use.

Assays for anti-HCV antibodies are the mainstay of clinical testing for HCV infection. Non-neutralizing antibodies to HCV can be detected by enzyme-linked immunosorbent assays or recombinant immunoblot assays, with the latter generally being used as confirmatory tests. Although first-generation tests (enzyme-linked immunosorbent assays and recombinant immunoblot assays) have limited sensitivity, increases in the number of antigens from different regions of the HCV genome in second-generation assays have increased sensitivity and shortened the period between exposure and seroconversion to as little as 4 wk (990). Recently available third-generation tests incorporate an additional recombinant antigen from the NS5 region of the genome and are expected to further improve sensitivity (991).

Detection of HCV RNA by reverse transcription-PCR has been used to identify patients with active viral replication (992–994). HCV RNA often appears in the serum within 1 wk after infection, well before the development of anti-HCV antibodies. Problems associated with PCR assays include both

Table 47. Other infections

Incidence	Measles, mumps, rubella, diphtheria, tetanus, pertussis, and polio are very uncommon. <i>Haemophilus influenzae</i> is a common pathogen in children, and is not unusual in immunocompromised adults. <i>Varicella</i> is very common. The incidences of both <i>H. influenzae</i> and <i>Varicella</i> infections are decreasing after widespread immunization programs.
Consequences	Infections are often life-threatening for transplant recipients.
Rationale	Vaccines that do not use live-attenuated viruses are safe. Although immunity may be less regularly achieved and may be of shorter duration in transplant recipients, compared with the general population, vaccination is usually effective.
Recommendations	Immunizations should be administered according to existing guidelines, with the exception that live-attenuated vaccines should be avoided for transplant recipients until controlled studies are completed (B).

false-negative and false-positive results (995–997), as well as limited availability in many clinical settings. For PCR-positive patients, measurement of the serum viral titer and identification of the viral subtype can be attempted. Both the branched-chain DNA assay and quantitative PCR assays have been used to measure HCV RNA levels in serum (992,998,999). The branched-chain DNA assay is less sensitive than the reverse transcription-PCR assays but is simple, automated, and reproducible. The identification of HCV subtypes requires either sequence analysis of the viral genome by PCR using subtype-specific primers (1000–1004), restriction fragment length polymorphism analysis (1005), or the line-probe assay (1006). Two recent prospective studies failed to find any association between HCV viral replication and the histologic progression of liver disease, after follow-up periods of 28 and 81 mo (1007,1008). Therefore, there currently appears to be no indication for the routine testing of viral replication in HCV-positive renal transplant recipients.

Other Infections (Table 47)

Incidence. The incidences of measles, mumps, rubella, diphtheria, tetanus, pertussis, and polio are very low, largely because of successful vaccination campaigns. However, some of these rare diseases are becoming more common, and infections are likely to be more severe in immunocompromised transplant recipients, compared with the general population (1009–1011). *Haemophilus influenzae* was a common pathogen in children, but the incidence of *H. influenzae* infections among children decreased dramatically after the introduction of a successful vaccine. *Varicella zoster* infections have been very common in adults and children. For example, in one study the incidence of *Varicella* infections among nonimmunized children and adolescents after renal transplantation was 22 of 49 cases (45%) (1012). However, successful vaccination with an attenuated live *Varicella* vaccine before transplantation has led to a recent decrease in the incidence of *Varicella* infections after transplantation (1012).

Consequences. All of the aforementioned infections are potentially life-threatening in immunocompromised patients.

Rationale. The measles, mumps, and rubella (MMR) vaccine is made of live-attenuated viruses. Individuals born before 1957 are advised to receive a two-dose MMR vaccination (1013). A series of immunizations with diphtheria and tetanus toxoids and acellular pertussis are recommended for infants (1014). A tetanus toxoid/diphtheria booster should be administered every 10 yr. It is generally recommended that all children be immunized with inactivated *H. influenzae* type b. Adults who may be susceptible to infection with encapsulated organisms, such as asplenic individuals, should also be considered for immunization against *H. influenzae*. Until recently, the oral poliovirus vaccine (OPV), an attenuated virus, was used almost exclusively. More recent recommendations include the use of inactivated poliovirus vaccine (IPV), which is somewhat less effective but carries less risk of vaccine-associated poliomyelitis (1015). This change in emphasis in the United States also reflects the fact that there have been no recent cases of poliomyelitis in the western hemisphere. In the

United States, immunization is recommended for all children and for adults who were not immunized as children. Booster injections may be administered to individuals planning travel to areas where infection poses a risk. Live-attenuated *V. zoster* vaccine can be administered to children at 12 to 18 mo. Children without reliable histories of *Varicella* infection should be vaccinated once if ≤ 12 yr of age and twice (4 to 8 wk apart) if ≥ 13 yr of age.

When possible, patients should be immunized before transplantation, according to existing guidelines and schedules (839,1013–1018). However, immunization is not always performed before transplantation, and studies have demonstrated that most immunizations produce a reasonable antibody response in the majority of transplant recipients (1012,1019–1023). Nevertheless, immunization is likely to be less effective in immunosuppressed renal transplant recipients than in the general population. The response rate is likely to be lowest when doses of immunosuppressive medications are high, such as in the first few weeks after transplantation or during treatment for acute rejection.

It is possible that live-attenuated vaccines can cause disease in very immunosuppressed patients. For example, there have been case reports of vaccine-associated measles deaths among severely immunosuppressed patients (1024,1025). The Centers for Disease Control and Prevention recommend that the MMR vaccine not be administered to severely immunocompromised patients but that close contacts of such patients should receive immunizations, to reduce the risk of exposure for the nonimmunized patients (1013). Similarly, the Centers for Disease Control and Prevention recommend that OPV not be administered to immunosuppressed patients (1015). However, IPV can be administered to transplant recipients. Indeed, in a recent study from Germany, IPV was administered to 164 adult renal transplant recipients; there were no major adverse effects (1020). *Varicella* vaccine is also a live-attenuated virus and has been administered to small numbers of children after renal transplantation without major adverse effects (1023). The diphtheria/tetanus vaccine is both safe and efficacious when administered after renal transplantation (1019,1020). Similarly, *H. influenzae* type b vaccine appears to be safe and effective when administered after renal transplantation (1021).

A questionnaire on immunization practices for children was sent to members of the North American Pediatric Renal Transplant Cooperative Study, and 62% of the centers responded (855). Standard killed vaccines, e.g., diphtheria and tetanus toxoids and acellular pertussis and *H. influenzae* vaccine, were recommended at 86% of the responding centers. Live-attenuated vaccines, e.g., OPV, MMR, and *Varicella* vaccine, were recommended at only 5 to 12% of the centers (855).

Immunizations should be administered according to existing guidelines. However, live-attenuated vaccines should generally be avoided for transplant recipients, especially for patients receiving high doses of immunosuppressive medications. An exception may be the *Varicella* vaccine, which has been reported by some to be safe for renal transplant recipients receiving standard maintenance immunosuppressive therapy.

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